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ANNALS OF SAUDI MEDICINE

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The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

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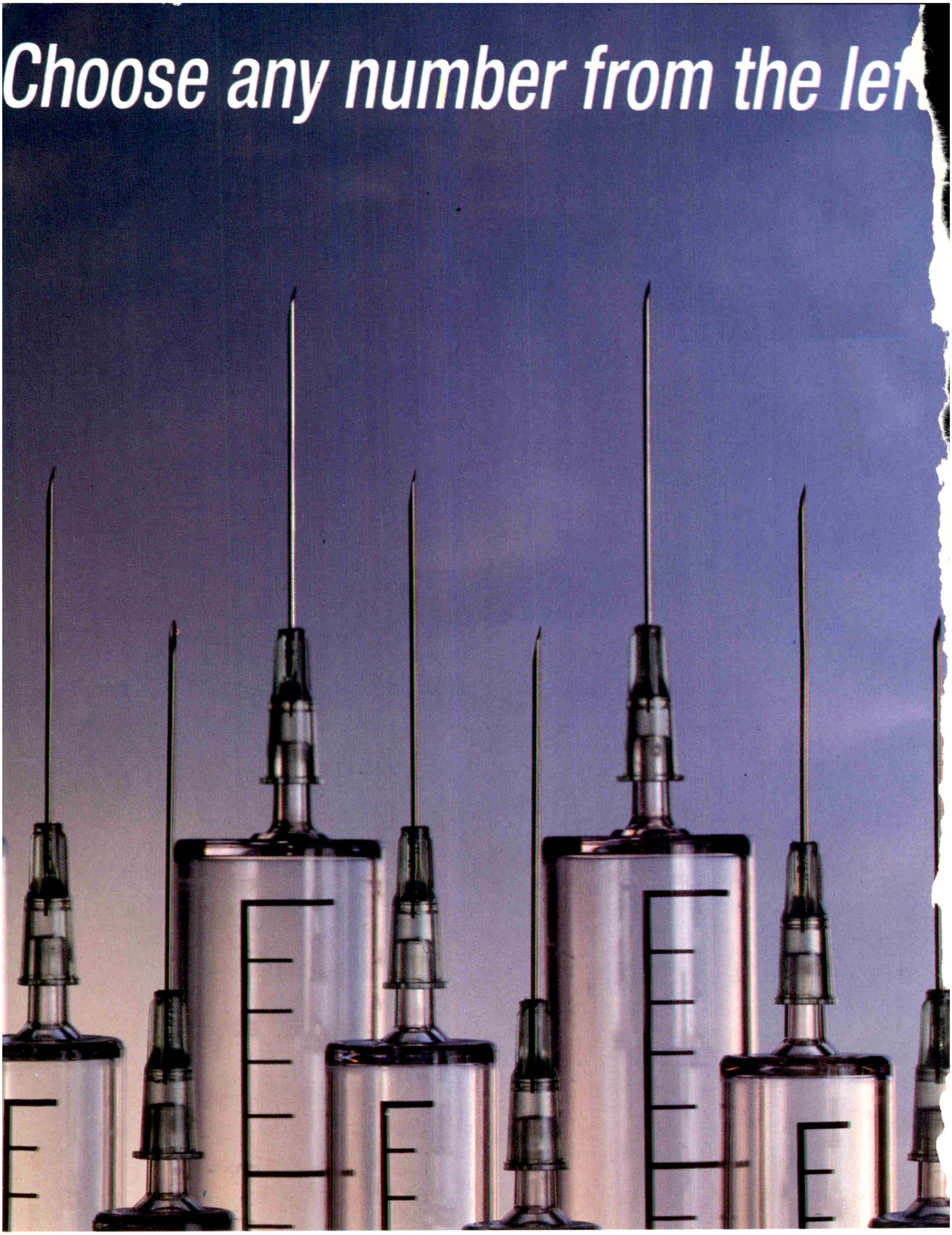

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ıonths: 30mg/kg* AUGMENTIN every 12 hours in premature infants and in full term infants during the perinatal period, increasing to 8 hourly intervals thereafter. *Each 30mg AUGMENTIN intrav
ontains 25mg amoxycillin and 5mg clavulanic acid. Treatment with AUGMENTIN should not be extended beyond 14 days without review. **CONTRA-INDICATION.** Penicillin hypersensitivity. **PRECAUT**
hanges in liver function tests have been observed in some patients receiving AUGMENTIN. The clinical significance of these changes is uncertain but intravenous AUGMENTIN should be used wit
patients with evidence of severe hepatic dysfunction. In patients with moderate or severe renal impairment AUGMENTIN dosage should be adjusted as recommended in the Package Insert L
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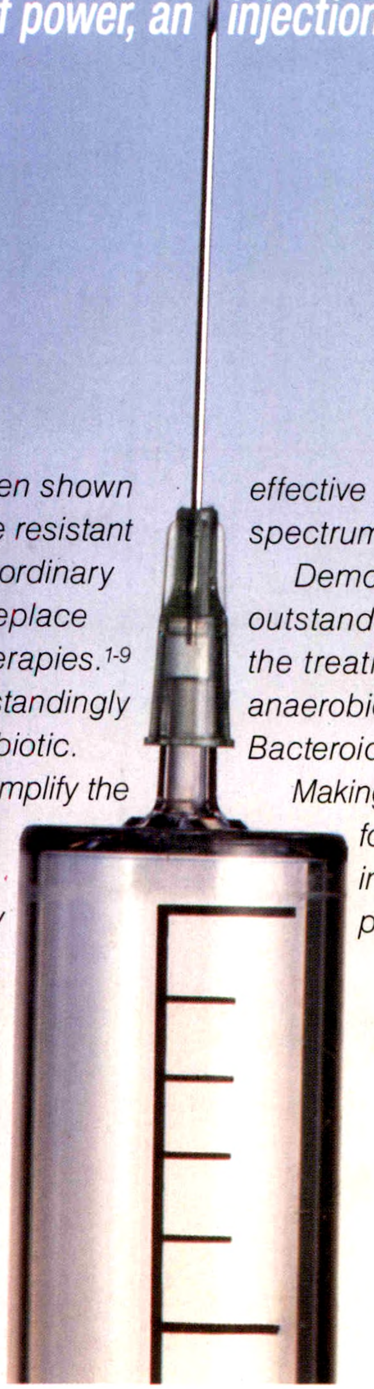

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ɔdidiasis have been reported. Phlebitis at the site of injection has also been reported. Urticarial and erythematous rashes sometimes occur but their incidence has been particularly low in clinic
n urticarial rash suggests penicillin hypersensitivity and treatment should be discontinued. Erythematous rashes are frequently mild and transient but may be severe when associated with infectiou
ıcleosis, in which case treatment should be discontinued. Rare cases of erythema multiforme, Stevens-Johnson syndrome and an occasional case of exfoliative dermatitis have been reporte
and occasionally fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema have been reported in patients on penicillin therapy. These reactions are more likely to occur in individua
ıistory of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Hepatitis and cholestatic jaundice have been reported. **AVAILABILITY.** *600mg AUGMENTIN intravenous vial*
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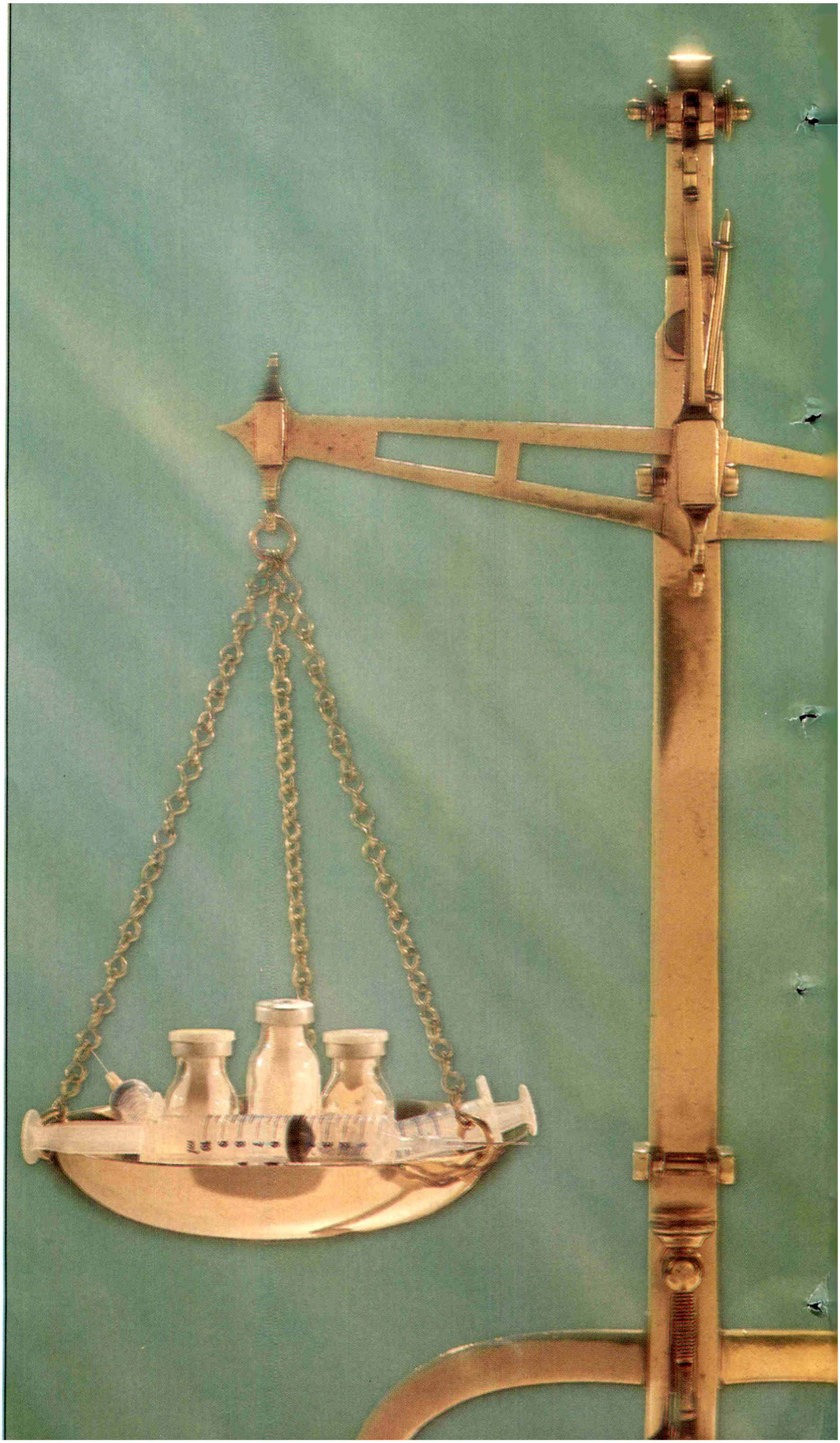

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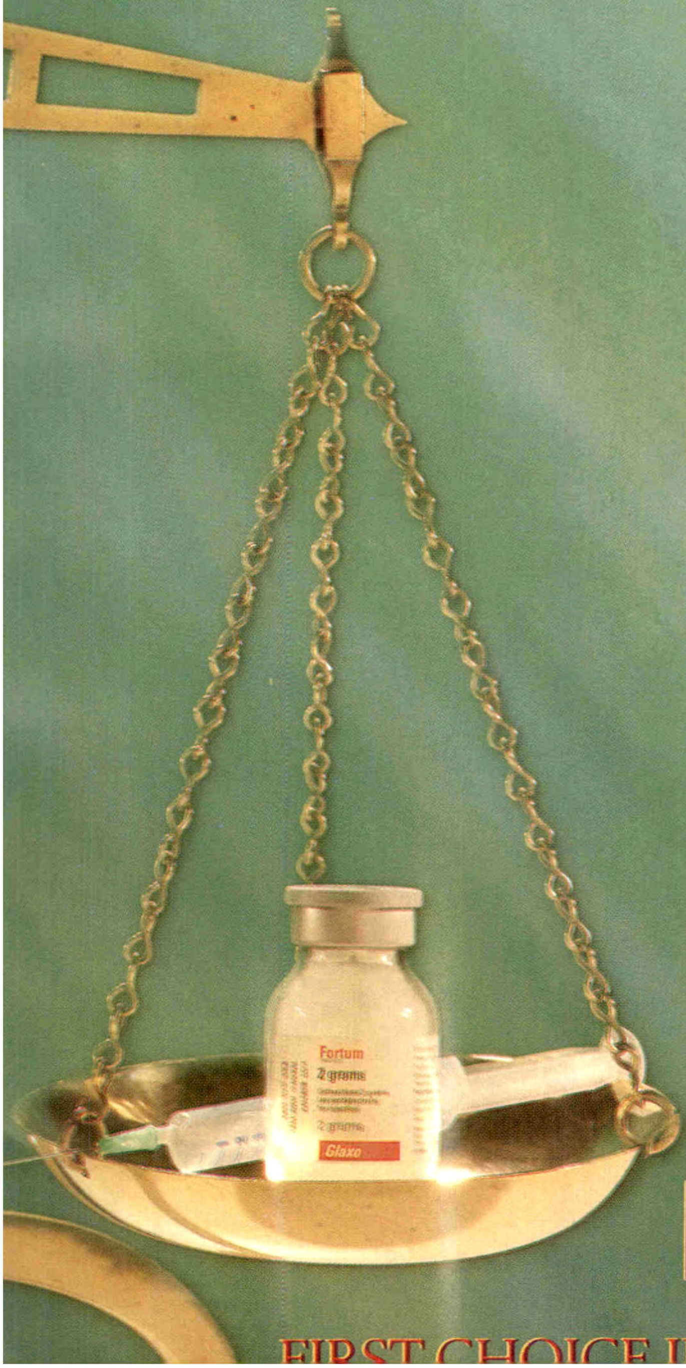

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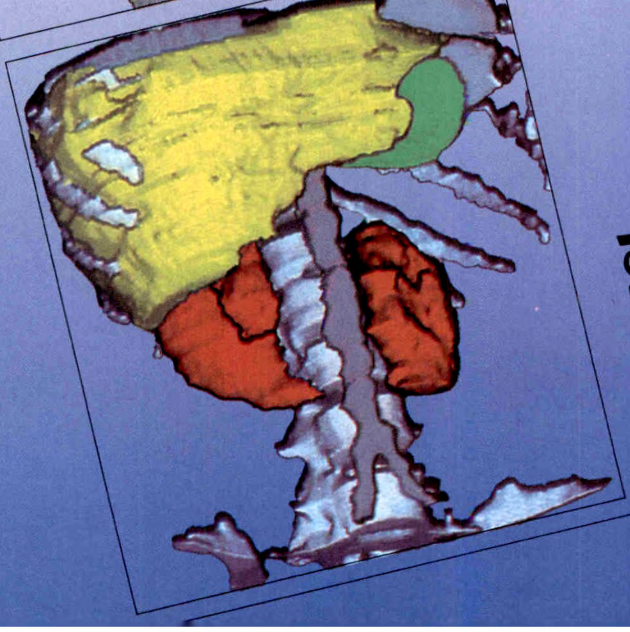

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Editorial

NEONATAL SCREENING NATIONWIDE?

In the first article of this issue Abu-Osba et al [1] describe their experience in the establishment and implementation of a neonatal screening program which has now been running for more than a decade at the Arabian American Oil Company (ARAMCO). The conditions included were hypothyroidism and phenylketonuria (PKU) which are commonly screened for in other countries and also abnormal hemoglobins, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and blood group incompatibility which were of particular interest to the study population.

The principle of neonatal screening is a universally accepted dogma in the philosophy of modern health care planning which emphasizes prevention as being more important than cure. While it is easy for the decision makers to accept national screening as a desirable service, it is more difficult for them to assign a priority to this package of health care among the competing bids of both high and low technology projects that will improve the well-being of the nation. One of the problems that will keep neonatal screening shuffled towards the bottom of the project pile is communication. The successful implementation of any screening program depends not only on efficient and comprehensive collection of specimens, transport and laboratory processing but also on access to the patient, or in our example, the parents for prompt recall for further testing or therapy as indicated. In the ARAMCO study, cord blood was used for thyroid and hematological screening but not for phenylketonuria where postnatal feeding needs to be established and a heelprick sample collected at 48 hours of age. Such an approach might not be feasible in some hospitals where it is routine for mother and child to be discharged within hours rather than days of delivery. This may not be so serious a problem for Saudi Arabia as it first seems. The prevalence of hypothyroidism in the ARAMCO study was approximately 1/3500 livebirths, similar to that reported in studies carried out in other countries but no case of phenylketonuria was detected, raising the possibility that classical PKU is less common in the Kingdom than elsewhere. If this is true, omission of PKU from a national screening program for logistic reasons would have less adverse societal impact than might be expected. Discounting the small but unknown fraction of births that take place without recognized professional attention there is still the chasm between the client and health care giver which every hospital doctor in the Kingdom has experienced when he wants to find a patient in a hurry. In this respect circumstances favored the ARAMCO workers who had easy access to all their clientele whose whereabouts were stored on computer.

The association of demographic and medical information enabled Abu-Osba et al [1] to make analyses of possible prevalence of different conditions by the place of origin of the family which has implications beyond those associated with neonatal screening per se. There was a tenfold change in the incidence of all abnormal hemoglobins which ranged from 6% to 60% depending on the place of the original family residence. Similarly the figures for G-6-PD deficiency varied widely, the overall average was 18% but the geographic range was as low as 1% in Abha and as high as 44% in Al-Qudayh. Because of the retrospective and uncontrolled nature of the data collection, these figures do not necessarily reflect quantitatively what happens in different parts of the country, but if they do indicate important geographic variations in the hematological make-up of the nation, they may stand as proxy for regional variation in heritable diseases. The discovery of a hemoglobinopathy or G-6-PD deficiency is important for the correct medical advice to be given to the individual but Mallouh and Abu-Osba [2] in a related study have found an unexpected association between G-6-PD deficiency and serious neonatal bacterial infections. The link may be direct but is more likely to be indirect with the blood disorder and increased susceptibility to infection both being expressed as indicators of a small gene pool. Both regional and national health care planners will be interested in the markers of disease patterns likely to be encountered in different parts of the country, half of whose population is less than 15 years old.

A national neonatal screening program has yet to be implemented in Saudi Arabia. Whether this is at first initiated at a regional or national level will be debated. The paper which has prompted this editorial is timely and important because the authors have been innovative in the relevant environment and have special local knowledge which can and should be harnessed by the authorities to initiate a larger neonatal screening program in the public sector.

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Originial Articles

COMPREHENSIVE NEWBORN SCREENING PROGRAM: ARAMCO EXPERIENCE, THE NATIONAL NEED AND RECOMMENDATIONS

Yousef K. Abu-Osba, MD; Ahmad Mallouh, MD; Mouhamed Salamah, MD;
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يوجد نقص في برامج التقصي الشامل للأمراض الولادية لدى المواليد على المستويين الوطني والإقليمي على حد سواء. أعدّ المركز الصحي التابع لشركة آرامكو في الظهران برنامج تقص شامل للمواليد تبعا للاحتياجات والموارد المتوفرة.. يتضمن هذا البرنامج تقصي قصور الدرقية الولادي وبيلة الفينل كيتون وشذوذات الخضاب وعوز خميرة غلوكوز ٦ ـ فوسفات نازعة الهيدروجين وتنافر زمر الدم. واجهتنا عدة مشاكل في أثناء التطبيق استدعت إدخال تعديلات عديدة على البرنامج. نصف في هذه المقالة تنظيم البرنامج وإجراءاته. تم تقصي حالات مايزيد على ٧٠ر٠٠٠ مولود منذ انطلاق البرنامج عام ١٩٨٠م وجمعت بيانات وبائية قيّمة كما تم الحصول على معلومات ضرورية للتطبيق السريري المباشر. إن من الممكن إعداد برنامج وطني لتقصي حالات الولدان في المملكة وهو أمر مطلوب على وجه السرعة. تتضمن المقالة توصيات مبنية على خبرة آرامكو في هذا المجال.

Comprehensive screening programs for congenital diseases of newborn infants are lacking at a national or regional level. A comprehensive newborn screening program modified to the needs and resources available was established in ARAMCO Dhahran Health Center. This program includes screening for congenital hypothyroidism, phenylketonuria, abnormal hemoglobins, glucose-6-phosphate dehydrogenase deficiency, and blood group incompatibilities. Several problems were encountered during the operation which required several modifications of the program. The organization and procedures of the program are described. Since the program was started in 1980, more than 70,000 newborn infants have been screened. Valuable epidemiological data have been collected and necessary information for direct clinical use was obtained. A national program to screen all neonates in the Kingdom of Saudi Arabia is achievable and urgently needed. Recommendations based on ARAMCO experience are given.

Screening programs for congenital diseases of newborn infants have been in effect for several decades in some countries. More than 30 diseases can be screened for in the neonatal period, and this list is growing [1–6]. Developing countries lack newborn screening programs for various reasons. But which diseases should be screened for and what is the priority? A major obstacle is lack of knowledge of the accurate incidence and the natural history of such diseases in the developing countries including Saudi Arabia. Sickle cell disease is a good example in which the clinical history varies in different geographical areas [7–15]. In newborn infants and children, an increased incidence of sepsis and serious infections in association with glucose-6-phosphate dehydrogenase deficiency and abnormal hemoglobins has been documented [16–19]. Peculiar clinical presentation and the incidence of hemoglobin H disease in the neonatal period has been described in Saudi Arab infants [20].

Health care has greatly improved in the last decades in the Kingdom. Now is the time to put effort into the campaign of controlling and preventing some potentially disastrous genetic dis-

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eases. Such comprehensive screening programs are lacking at the national or regional level, although a screening program for congenital hypothyroidism has been started by the Ministry of Health. The cost/benefit effectiveness of neonatal screening has been established. Regionalization, automation and testing a single specimen for several defects simultaneously will decrease the cost in a comprehensive genetic screening program even further. Several problems and obstacles face the establishment of a newborn screening program for the whole Kingdom. These can be summarized in the following: manpower, technical expertise, time of sample collection, confirmation, treatment and follow-up, and appropriate funds to run the program. The following options are available to establish a mass screening program for the Kingdom: affiliation with an established program which is costly and time consuming, or establishing/designating a central laboratory in every region which is more cost effective with less delays in diagnosis.

ARAMCO Newborn Screening Program Experience

Arabian American Oil Company (ARAMCO) Medical Organization provides the medical care for 50 to 60,000 employees and their dependents in several health care facilities and a major referral hospital (Dhahran Health Center). ARAMCO established the first comprehensive neonatal screening program in the Kingdom in October 1980 [21]. This program includes screening for congenital hypothyroidism, phenylketonuria, abnormal hemoglobins, glucose-6-phosphate dehydrogenase, and blood group incompatibilities. The total number of newborn infants born in ARAMCO medical care facilities ranges between 6,000 to 8,000 deliveries per year. More than 70,000 newborn infants have been screened so far in this program which is the largest and most comprehensive in the country. ARAMCO employees come from more than 32 countries. More than 90% of the newborn infants are Saudi Arabs whose families come from the whole country from Najran to Dammam. The personnel computer files are coded for the family original residence and nationality thus facilitating the analysis of the results.

Organization and Procedures of ARAMCO NSP

Blood Sample Collection

Midwives or physicians attending deliveries collect blood samples from the cord and laboratory technicians or nurses collect venous capillary blood samples according to standard procedures from babies who were delivered in hospital or at home, respectively. Both cord blood and capillary or venous samples are suitable for testing for blood group incompatibility, abnormal hemoglobins, G-6-PD and congenital hypothyroidism. Heel stick sample on a filter paper after 48-hours feeding or at the time of discharge from the hospital were collected for PKU. Infants born at home were tested during hospitalization or their first visit to the clinic.

Sample Processing

All blood samples were labelled and transported to Dhahran Medical Laboratory where all tests were performed. A copy of the results was distributed to each of the medical records of the outpatient file, screening physician and the coordinator of screening program. All results were entered in a specially designed computer program for analysis. Subsequently, all results were available in a computer terminal in all ARAMCO clinics which provide direct and easy access to the results.

Laboratory Methods

G-6-PD deficiency in red blood cells was tested as described by Beutler and Mitchell [22]. Total serum thyroxine was determined by radioimmunoassay using a comercially available kit (Tetra-Tab RIA), Nuclear-Medical Laboratories, Inc., Dallas, Texas, USA. Thyroid stimulating hormone was measured by radioimmunoassay for all infants with cord blood thyroxine value of two standard deviations below the mean for all the tests performed. Abnormal hemoglobins were tested for by screening hemoglobin electrophoresis and quantitative confirmatory tests were utilized to verify hemoglobin migrating in the same area as S, C, H, and Bart's. Blood typing was done by the slide and tube procedures. Phenylketonuria was tested for by Guthrie method [23]. Quality control for all tests was performed.

Coordination of Patient Care

A manual was developed defining the goals, policies, procedures, methods, treatment and follow-up, personnel responsibilities and quality control (available at King Faisal Specialist Hospital and Research Centre Medical Library) [24]. The primary responsibility was carried out by a designated physician in every medical care facility. A hematologist, endocrinologist, and a developmental pediatrician were available for consultation and follow-up. A coordinator for the entire screening program had the following responsibilities: (1) reviews the newborn screening program policies and procedures and revises them if necessary, (2) performs statistical analysis of the results, (3) provides guidance to the physicians and nurses with regard to the program, (4) initiates a quality assurance program, (5) maintains the newborn screening program manual; reviewing, revising and updating.

Results of ARAMCO NSP

Since the ARAMCO newborn screening program was started in 1980 more than 70,000 newborn infants have been screened. The following is an overview of the preliminary analysis of the first 35,000 infants.

Abnormal Hemoglobins

The incidence of all abnormal hemoglobins (Abn Hb) in Saudi Arab neonates varied significantly from one original family residence to another (Table 1). In Um Al-Hamam, it was as high as 62.8%, in Abha as low as 6.7%, and Riyadh 12.5%. Sickle cell hemoglobin (Hb S) incidence for all Saudi Arab neonates screened was 14.4% and ranged from 0.8% in Najran to 26.4% in Al-Qudayh. Hb S was present in association with various other hemoglobins, sickle cell disease was present in 1.37% and sickle cell trait in 13.1% of all infants (Figure 1). Bart's hemoglobin (Hb B) incidence in all infants screened was 17.8%, ranging between 4.7% in Najran to 36.3% in Al-Awwamiyah, Hb B was present in association with various other hemoglobins, incidence of alpha thalassemia syndromes was 17.3% and probable beta thalassemia 0.5% (Figure 2). Some rare hemoglobins such as Hb C and Hb E were also found (Figure 3).

TABLE 1. *Incidence of all abnormal hemoglobins in Saudi Arab neonates.*

Location	Total Number screened	Abnormal hemoglobin (%)
Hofuf	3,025	32.33
Gatif	2,747	52.35
Um Al-Hamam	339	62.83
Safwa	1,846	49.19
Abqaiq	958	12.63
Bilad Ghamid	105	7.62
Abha	105	6.67
Zahran	41	12.20
Jizan	13	46.15
Yanbu	22	27.27
Jiddah	45	15.56
Baljurashi	62	12.90
Hayil	198	10.10
Khamis Mushayt	48	8.33
Najran	423	12.53

Results of non-Saudi Arabs from various nationalities also showed variable incidences of abnormal hemoglobins (Table 2). Although the number screened from these countries was small; sickle cell and Bart's hemoglobins were found in neonates from Jordan, Lebanon, Egypt, Pakistan and Sudan. Hemoglobin E was found in neonates from Pakistan and Egypt. It is of interest to observe the high incidence of hemoglobin F in neonates from Pakistan (3.79%) only.

Blood Groups

The pattern of blood groups was different in the Saudi Arab newborn infants from that of white Americans and all other nationalities as a group (Figure 4).

G-6-PD Deficiency

G-6-PD deficiency was present in 24% of all the males and in 12% of all the females, ranged from 1.26% in Abha, 2.59% in Riyadh and 11.59% in Bilad Ghamid to 43.8% in Al-Qudayh (Figure 5). G-6-PD deficiency was also present in neonates from other countries: Jordan 1%, Pakistan 1.2%, Sudan 1.3% and Philippines 1.8%.

Congenital Hypothyroidism

Cord blood T_4 was 10.3 ± 2.2 mcg/dl (X ± SD) in the Saudi Arab neonates which was not significantly different from other nationalities (Table 3). The incidence of congenital hypothyroidism was approximately 1/3500 live newborn, similar to what has been reported in literature [25,26]. In infants with congenital hypothyroidism T_4 values were 4.3 ± 1.4 mcg/dl (X ± SD), and TSH 278 ± 138.3 mciu/dl. Clinical presentation, treatment and long term follow up are under preparation. No cases of PKU were discovered through the screening program. Details of the analysis for the

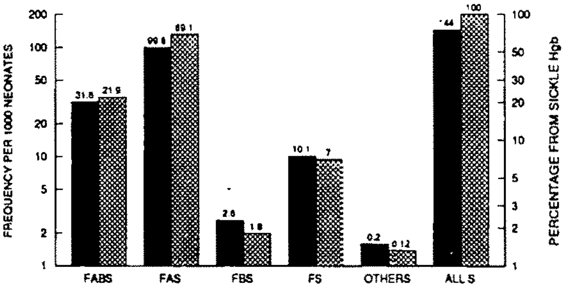

FIGURE 1. Hemoglobins associated with sickle cell hemoglobin in Saudi Arab neonates.

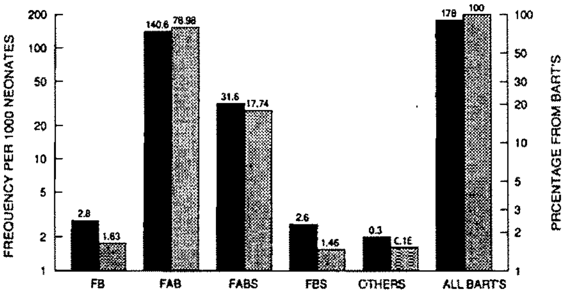

FIGURE 2. Hemoglobins associated with Bart's hemoglobin in Saudi Arab neonates.

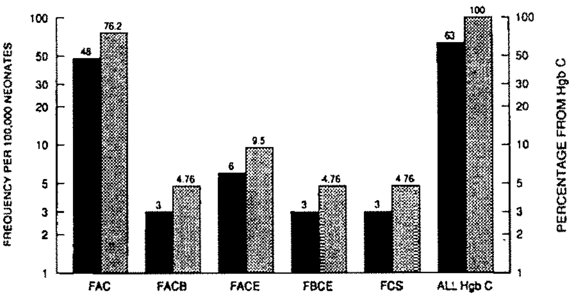

FIGURE 3. Hemoglobins associated with hemoglobin C in Saudi Arab neonates.

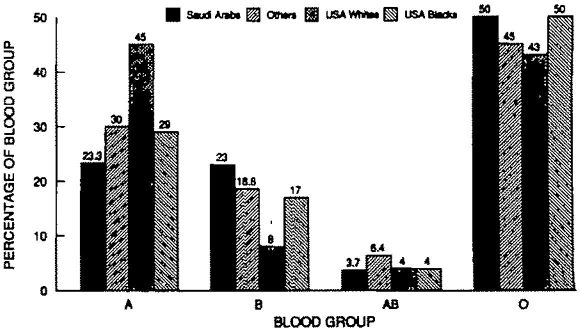

FIGURE 4. Blood groups in newborn infants from various countries.

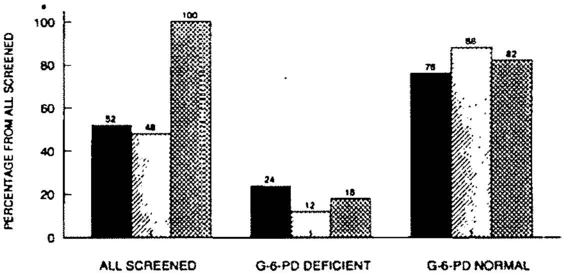

FIGURE 5. Incidence of glucose-6-phosphatase dehydrogenase deficiency in Saudi Arab neonates.

TABLE 2. *Umbilical cord blood screening hemoglobin electrophoresis of neonates of Middle Eastern countries other than Saudi Arabia.*

	Jordan		Lebanon		Egypt		Pakistan		Sudan	
Hb	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
FA	295	97.68	116	98.3	48	90.0	396	93.83	225	96.15
FAS	3	1.0	1	0.85	1	1.0	2	0.47	5	2.14
FACE	0	0	0	0	0	0	1	0.23	0	0
FAB	2	0.66	0	0	3	5.66	5	1.18	1	0.43
FS	0	0	0	0	0	0	0	0	1	0.43
F	2	0.66	1	0.85	0	0	16	3.79	1	0.43
FAE	0	0	0	0	1	1.0	1	0.23	0	0
FADG	0	0	0	0	0	0	1	0.23	0	0
Total	302		118		53		422		233	

TABLE 3. *Umbilical cord blood T_4 values for various nationalities.*

	Umbilical cord blood T_4 (mcg/dl)			
Nationality	Mean	SD	Minimum	Maximum
Saudi Arabia	10.31	2.20	0.3	24.0
USA	10.60	2.05	1.1	19.8
Jordan	10.25	2.11	0.3	19.2
Lebanon	10.95	1.86	7.0	15.2
Egypt	10.50	2.15	6.1	15.1
India	10.56	2.34	4.1	19.0
Pakistan	10.20	2.19	4.7	19.5
Sudan	10.75	2.47	3.1	20.2

various villages and cities and the nationalities screened are available at King Faisal Specialist Hospital and Research Centre Medical Library [27]. Details of the analysis for various problems are under preparation.

Discussion

A comprehensive newborn screening program modified to the needs and resources available was established in ARAMCO Dhahran Health Center. Several problems were encountered during the investigation which required modifications to the program. Since the program was started in 1980, more than 70,000 newborn infants have been screened. Valuable epidemiological data have been collected and necessary information for direct clinical use obtained. A comprehensive national program to screen all neonates in the Kingdom of Saudi Arabia is achievable and urgently needed. Screening for congenital hypothyroidism, which was started by the Ministry of Health, is an important step in the right direction, but other congenital problems such as hemoglobinopathies and G-6-PD deficiency is equally important. The fast and dynamic internal immigration and mixing of the population make it inaccurate to extrapolate the results of any small scale screening program in a particular geographical area to the community at large. The plans for a comprehensive national screening program should take into consideration the multiple health care systems present in the Kingdom, and wide scatter of the population. This national program can be subdivided into smaller regional programs according to the geographical distribution of the population and/or according to the various health care organizations. Due to the limited number of human resources and problems related to technology transfer and the cost of establishing such programs, a joint plan among the various medical health organizations in the Kingdom can be adopted and modified according to the circumstances and needs of each organization. Such a plan will define the program's objectives, procedures, operational plans, quality assurance, statistical analysis and evaluation.

A central laboratory affiliated with one of the universities or Ministry of Health to perform the sophisticated confirmatory tests for all the Kingdom should serve as a reference central laboratory. A computerized program for entering the data, reporting and analysis will serve in obtaining accurate epidemiological statistics and rapid reporting, treatment and follow-up.

Acknowledment

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FETAL BIOPHYSICAL PROFILE MONITORING AND PERINATALOUTCOME

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أجريت دراسة استطلاعية على مائة وتسع حالات من الحمل المحفوف بالمخاطر وأجري للأجنة ٢٧٩ فحصا لاختبار السيماء الفيزيائية الحيوية بلغت جدواها التكهنية ايجابًا أو سلبًا نسبة ١٠٠٪ و ٧١٫٤٪ على التوالي عند آخر اختبار للسيماء الفيزيائية الحيوية قبل الولادة. أيدت نتائج هذه الدراسة نتائج سابقة بوجود علاقة وثيقة بين كون نتائج الفحص طبيعية وتمام الولادة على نحو مُرض. إن عدم حدوث الوفاة إبّان الولادة وفي خلال أسبوع واحد من النتائج الطبيعية لاختبار السيماء الفيزيائية الحيوية على الجنين، والذي يتوافق أيضا مع نتائج الدراسات الأخرى، يؤكد القيمة المطمئنة لظهور نتائج طبيعية للاختبار. إن ارتفاع جدوى التكهن الإيجابي في دراستنا قد يكون ناجما عن عوامل متعددة، بما في ذلك اتباع خطة تضمن تعيير حالات المرضى قبل إجراء الاختبار وكذلك تكرار الاختبار عند ظهور نتائج غير مطمئنة. يعتبر اختبار السيماء الفيزيائة الحيوية للجنين إجراءً مبسطًا ومضمونًا وذا جدوى في تدبير حالات الحمل المحفوف بالمخاطر. وتظهر قيمته الأساسية فيما يبدو في الإقلال من عدد اللواتي يعتبر حملهن محفوفا بالمخاطر وقد يُدخلن إلى المستشفى اعتمادًا على الظواهر السريرية فقط.

A prospective study of 109 high risk pregnancies on whom 279 fetal biophysical profile (FBP) examinations were performed showed positive and negative predictive values of 100% and 71.4%, respectively in the last FBP examination prior to delivery. The study confirmed other reports in the literature of a high correlation between normal examination and satisfactory perinatal outcome. The absence of perinatal mortality within one week of a normal FBP examination, which was also in agreement with other reported studies, reaffirms the reassuring nature of a normal examination. The high positive predictive value in our study may be due to several factors, including the use of a protocol which ensured standardization of the patient's condition prior to examination as well as repeat evaluations after non-reassuring tests. FBP evaluation is considered a simple, reliable and useful examination for the management of high risk pregnancies. Its main value would appear to be a reduction in the number of high risk pregnancy patients who would otherwise have been admitted on the basis of the clinical findings.

Fetal asphyxia causes approximately half of stillbirth [1–4] and often manifest with intrauterine growth retardation. It also contributes significantly to perinatal mortality and morbidity. Therefore, the recognition and monitoring of the fetus at risk cannot be over emphasized.

With the advent of static and realtime ultrasonography the evaluation of the fetus progressed from the mere acquisition of the fetal age to detection of fetal anomalies and subsequently to a direct physical examination of the fetus–fetal biophysical profile (FBP). Several authors [3–7] have shown the superiority of fetal biophysical profile (FBP) consisting basically of fetal heart rate reactivity (FR), fetal breathing movements (FBM), fetal movement (FM), fetal tone (FT), and qualitative amniotic fluid volume (AFV) as compared with any other single test in monitoring the fetus at risk. A score criteria whereby eight or more was considered normal while seven or less suggested a fetus at risk was used [3–7]. However, Vintzileos et al [8] expressed the use and misuse of

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the fetal biophysical profile and emphasized the value of the score components in order to reduce false positive and false negative rates. Manning et al [9] in a recent communication also demonstrated the inequality of the various score components and showed that predictive accuracy is related to score composition.

We wish to report our experience on a prospective study on 109 consecutive high risk pregnancies in which the results of the FBP are compared with the perinatal outcome as judged by the presence or absence of fetal distress in labor, neonatal one minute Apgar score and perinatal mortality. We do not have any report of such work done in this environment as of now.

Material and Methods

One hundred nine (109) patients with high risk pregnancies as listed in Table 1 provided the material for this study. The gestational age was between 29 and 44 weeks. The cases with intrauterine growth retardation qualified for inclusion if they had reliable dates confirmed in early pregnancy and fundal height less than expected for gestational age. Ultrasonically these patients also had over three weeks less than the mean growth parameters and/or lack of fetal growth with successive ultrasonic evaluation.

The protocol used, aimed at standardization of the maternal state, was modified from Lawrence et al [10]. The patients should thus be in a restful or sedentary state for at least one hour, postprandial for one to two hours, not smoke for at least two hours nor receive analgesic or sedative for at least four hours. Any drugs which might affect the examination was recorded.

A realtime ultrasound machine (Siemens Sonoline SL-2 model) with a 3.5 MHz sector transducer and incorporating an M mode for evaluation of fetal heart rate was used for the study. Each variable was given a score of 2, 1 or 0 using the scoring criteria as modified by Vintzileos et al [6] and shown in Table 2.

Fetal reactivity as monitored by ultrasound examination was used in place of non-stress test although some patients had cardiotocography before reporting for the assessment. Fetal reactivity was defined as fetal heart rate acceleration of at least 15 beats per minute lasting 15 seconds in association with fetal movements. Ultrasonically the heart rate was measured at various times during the examination and often after observations of fetal motion. Over two variations within the heart rate of up to 15 beats per minute within the 30 minute period was considered as normal. Breathing movement and gross body movement (trunk and limbs) were observed in the sagittal view. A breathing movement was defined as a paradoxical movement of the fetal thorax and abdomen. Fetal movement was considered as simultaneous movement of trunk and limbs vigorous enough to obscure breathing movement.

Fetal tone was judged by observation of at least one episode of extension of extremities with return to flexion and also one episode of extension of spine with return to flexion.

Qualitative evaluation of amniotic fluid volume (AFV) was performed by measurement of pockets of amniotic fluid after ensuring that such pockets were free of the umbilical cord so as to avoid false estimations. The transducer was kept at right angle to the contour of the uterine wall and measurement of the fluid pocket was taken in two perpendicular planes.

General examination included placental localization, cord examination and exclusion of congenital anomalies. A minimum of 30 minutes was used for each examination with the exception of two cases of non-reassuring tests where the examinations were extended to 90 minutes to differentiate fetal sleep cycles from true abnormal tests. The examination and scoring were done by two observers and the interval between tests was individualized according to circumstances ranging from daily to once or twice weekly.

Perinatal outcome was evaluated by the presence or absence of any one of the following: fetal distress in labor, abnormal neonatal 1 minute Apgar score (defined as a score less than seven) and perinatal mortality.

Results

A total of 279 examinations were performed on 109 patients. Of the 279 examinations, 241 (86.5%) were normal (FBP score of 8 to 10), ten (3.5%) were equivocal (FBP score of 7), and 28 (10%) were abnormal (FBP score of 0 to 6).

The clinical data of these patients are shown in

Table 1. They were all high risk pregnancies with intrauterine growth retardation (IUGR) contributing 61% of the total, followed by patients with non-reactive CTG (14%).

TABLE 1. *Clinical data of patients studied (FBP).*

Intrauterine growth retardation (IUGR)	67
Non-reactive cardiotocography (CTG)	15
Prolonged pregnancy	6
Pre-eclampsia	6
Congenital fetal anomaly	5
Maternal hypertension	4
Maternal diabetes mellitus	4
Multiple pregnancy	2
Total	109

The range of gestational age was 29 to 44 weeks with a mean of 37 weeks.

Table 2 presents findings of the last examination prior to delivery. These were usually performed within 24 hours to one week of delivery. In 109 patients studied, 91 (83.4%) had normal FBP and on delivery the babies had normal Apgar scores. However, one of these had hydrocephalus and polyhydramnios and the FBP was normal during all the follow-up studies which included monitoring of the ventriculohemispheric ratio. The fetus was delivered at 38 weeks and ventricular shunt was inserted. Four patients (3.6%) had equivocal scores. One of these was a pre-eclamptic patient whose FBP study showed absent fetal tone and decreased gross body movement with a

TABLE 2. *Fetal biophysical profile score.*

Variable	Score 2	Score 1	Score 0
Fetal breathing (FBM)	One episode lasting at least 60 sec within 30 min	One episode lasting 30–60 sec within 30 min	No breathing movement or breathing movements less than 30 sec within 30 min
Fetal reactivity (FR)	Definite reactivity (over 2 acceleration in 30 min)	Equivocal reactivity (1 or 2 accelerations in 30 min)	No reactivity (no acceleration in 30 min)
Qualitative evaluation of amniotic fluid volume (AFV)	2 cm square or more	Between 1 cm and 2 cm	Less than 1 cm
Fetal tone	At least one episode involving both extremities and spine	At least one episode involving either extremities or spine	Extension movement of extremities not followed by return to flexion
Fetal movement (FM)	3 or more in 30 min	1 or 2 in 30 min	No movement in 30 min

TABLE 3. *Result of FBP study on 109 high risk pregnancies.*

FBP score		Perinatal outcome					
Score	Total number	Fetal distress in labor		Neonatal 1 minute Apgar score		Perinatal mortality	Congenital anomalies
		Yes	No	Abnormal	Normal		
8–10	91	0	91	0	91	0	1 hydrocephalus
7	4	1	3	1	3	0	1 bilateral hydronephrosis and IUGR
4–6	11	3	8	7*	4	2	3** multiple congenital anomalies
0–3	3	Stillbirth (IUGR)				3	2 multiple congenital anomalies

* Includes the 3 patients with fetal distress and also the 2 perinatal deaths.
** Includes the 2 perinatal deaths.

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score of seven. She subsequently developed fetal distress in labor. Another patient with equivocal FBP score had bilateral hydronephrosis earlier detected on ultrasound, confirmed in the neonatal period. The reason for FBP study was IUGR. This patient had reduced AFV and lack of FT.

A total of 14 patients (12.8%) had abnormal FBP score. Of these, three were stillborn with zero scores one of which was one of twins. The clinical presentation in all three cases was IUGR with reduced fetal movement. Severe oligohydramnios was found in all cases and in two of these who were subsequently confirmed to have multiple congenital anomalies, the renal and bladder outline were not seen at ultrasound. Eleven cases had scores of four to six and on delivery seven of these cases had abnormal one per minute Apgar score. Four patients had normal Apgar scores and normal perinatal outcome while one of those with abnormal Apgar score had an uneventful neonatal period. The breakdown of those with abnormal neonatal period is shown in Table 3.

Table 4 shows a correlation of the last FBP score with perinatal outcome. The specificity and sensitivity of the test (excluding the four patients with equivocal score) were each 100% while the negative and positive predictive values were 71.4% and 100%, respectively.

Table 5 shows the cummulative results of the FBP for antepartum fetal assessment in previous studies taken from the literature [11] compared with the current study.

TABLE 4. *Correlation of the last FBP score with perinatal outcome.**

	Perinatal outcome		
FBP Score	Normal (positive)	Abnormal (negative)	Total
Normal (positive)	91	0	91
Abnormal (negative)	4	10	14
Total	95	10	105

Sensitivity = 100%; specitivity = 100%; positive predictive value = 100%; negative predictive value = 71.4%.
* Excluding the 4 patients with equivocal FBP score.

Discussion

This study confirms the high correlation between a normal FBP study and satisfactory perinatal outcome as reported by several other authors [3–6]. The absence of a false negative finding in our study is also in agreement with the report of Vintzileos et al [6]. A false positive rate of 4.5% in our series is low compared with other

TABLE 5. *Cummulative results of fetal biophysical profile foantepartum fetal assessment.*

		Number of tests					Crude PNM		Corrected PNM*		False negative Rate**	
Study population	No. of patients	High risk (%)	Total	Normal	Equivocal	Abnormal	No.	Rate	No.	Rate	No.	Rate
Manitoba general population 1979–1982	65,979	20					943	14.1	586	8.81	–	–
Manitoba prospective study	12,620	100	26,257	97.52%	1.72%	0.76%	93	7.37	24	1.90	8	0.643
Baskett et al	2,400	100	5,618	97.1%	1.70%	1.2%	23	9.20	11	4.40	1	0.500
Platt et al+	286	100	1,112	94%	3.5%	2.4%	4	14.00	2	7.00	2	7.400
Schifrin et al+	158	"Most"	240	–	–	–	7	44.00	2	12.60	1	6.300
Vintzileos et al	150	100	342	94.9%	2%	3.1%	5	33.30	4	26.60	0	0
Total	15,614	90	33,569	95%	2%	1%	132	8.40	43	2.70	12	0.770
Makanjuola et al	109	100	279	86.5%	3.5%	10%	5	45.8	1	9	0	0

* The perinatal mortality (PNM) rate is corrected to exclude death due to lethal anomaly.
** Stillbirth within one week of a normal test result.

reports in the literature [12] but this can probably be attributed to the comparatively small population studied. However, standardization of the examination conditions, repeat evaluation following non-reassuring studies as well as patient selection may also have contributed to the high positive predictive value.

The pathophysiology of FBP is based on the concept that during fetal development, the developing central nervous system requires a high oxygen level for growth and for performing various biophysical activities. Although the sensitivity of the various areas to hypoxia is not well known, it is speculated that variations occur [6,8]. Also by the progressive asphyxia concept [8], the first centers to develop are the last to be affected. Hence, the fetal reactivity center which develops at about the 28th week is the first to be affected while the cortical area for tone which develops at about the eighth week is the last to be affected. Absence of fetal tone is therefore associated with a high perinatal mortality.

The variables used for FBP are of two kinds–the acute and the chronic markers [6,8]. The acute markers are FR, FBM, FT and FM while oligohydramnios is a chronic marker. A chronic hypoxic state is said to cause reduced blood flow to the lungs and kidneys and hence a reduction of amniotic fluid production in late pregancy. Also there is a high incidence of cord compression and intrauterine death in fetuses with oligohydramnios.

The significance of the score component is shown in two of our cases with an equivocal score of seven. The abnormal findings were in the FM and FT in a case which later developed fetal distress in labor and FT and AFV in another case with bilateral hydronephrosis. Abnormal FM, FT and AFV have been reported to have high correlation with unfavorable fetal outcome [12]. The morbid outcome in those with zero scores is consistent with the findings of Manning et al [13] who stated that the predictive accuracy of zero score using mortality and morbidity as end points was 100%.

Although it is generally recognized that the Apgar score is subject to many intrapartum events not related to the antepartum fetal condition, nonetheless reduced fetoplacental function makes the fetus more susceptible to intrapartum insults and the use of 1 minute Apgar score is still a valid measure of antepartum fetal well–being as compared to the 5 minute Apgar score which may be further influenced by resuscitative measures adopted postpartum.

An interesting finding in our study is the observation of fetal hyperactivity in the presence of polyhydramnios in three patients with hydrocephalus, diabetes mellitus and multiple pregnancy, respectively. All the fetuses in these cases had increased frequency of FT, FM and respiratory movements during successive evaluations. These findings may be due to a relative increase in available space for fetal movement and may result in false negative results.

Our normal test rate of 86.5% (Table 4) is less than other reported cases. This is probably due to the inclusion of two cases of intrauterine fetal death due to severe congenital anomalies. The population studied is also comparatively small. The same explanation also goes for the high abnormal FBP rate of 10%. Our high crude Perinatal Mortality Rate (PRM) is also due to perinatal deaths resulting from severe congenital anomalies as earlier indicated above.

The main value of fetal biophysical profile monitoring would appear to be a reduction in the number of our patients who would otherwise have been admitted on the basis of the clinical findings. Patients with completely normal FBP were managed largely on outpatient bases with weekly follow-up studies. A similar drop in antepartum patient admission has been reported by Baskett [12] and Manning et al [14].

It could be argued that a method of fetal assessment in which abnormal test results correlates with a high perinatal mortality is too late to be of clinical use. Thacker and Berkelman [15] acknowledged that using the results of the FBP in clinical management weakens the validity of the test, in particular its relationship to perinatal mortality. Pearson [16] also stated that "There are no early warning signs of perinatal asphyxia only late ones". FBP monitoring therefore falls short of the ideal test. However it may well be those cases with abnormal FBP score but with normal neonatal outcome were those who were promptly delivered before irreversible features of asphyxia occurred. Although the addition of other variables such as eye movement, sucking and urine production [12] may improve the predictive value, other tests aimed at a more accurate evaluation of the fetal environment such as uteroplacental and umbilical blood flow and fetal blood sampling, when possible, may be needed. Presently FBP monitoring offers a simple, reliable and useful guide for monitoring high risk pregnancy.

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DIABETES MELLITUS: KNOWLEDGE, ATTITUDE, PRACTICE AND THEIR RELATION TO DIABETES CONTROL IN FEMALE DIABETICS

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استقصينا في دراسة سريرية على مريضات السكري مدى إلمامهن بالداء وموقفهن منه وتقيدهن بالعلاج وعلاقة ذلك بضبط سكر الدم. اخترنا عشوائيًا ثلاثمائة امرأة سعودية يعانين من داء السكري ممن تجاوزن العشرين من العمر وذلك من سجل مركز أمراض السكري والغدد الصماء في مدينة الدمام في المنطقة الشرقية من المملكة العربية السعودية، كما جرت لهن مقابلات شخصية وفقا لاستبيان أعد مسبقا. تمت مقايسة الهموجلوبين المرتبط بالغلوكوز كمشعر لضبط سكر الدم باستخدام تقنية العمود الصغير، كانت النتائج العامة كما يلي: درجات متدنية بشكل شامل بالنسبة لمعرفة الداء والموقف منه والتقيد بالنظام العلاجي. كان متوسط الهموجلوبين المرتبط بالغلوكوز أعلى بدرجة هامة في النمط ١ من المرضى (السكري المعتمد على الأنسولين)‰(9.1± 2.0 6p= 0.001 تقترح الدلائل المستقاة من هذه الدراسة ضرورة تطبيق برنامج تعليمي مستمر وفعال لمرضى داء السكري بهدف زيادة وعيهم وإعطائهم دورا أكبر في علاج حالتهم معتمدين على أنفسهم. لذلك نوصي بأن تسند مسؤولية رعاية مرضى داء السكري أساسًا إلى مراكز الرعاية الأولية المزودة بأفراد مدربين تدريبا ملائما ومؤهلين ثقافيا وعلميا، ليعملوا بالتعاون مع مراكز خدمات الرعاية الثانوية الأخرى. إن المراقبة والمراجعة الطبية للعناية بمرضى داء السكري في مراكز الرعاية الصحية الأولية سوف تؤدي إلى تحسين الأداء السريري في هذا المجال.

In a clinic-based study, the extent to which diabetes knowledge, attitude and compliance related to glycemic control was explored. Three hundred Saudi diabetic women aged 20 years and above were randomly selected from the register of the Diabetes and Endocrine Centre in Dammam, in the Eastern Province of Saudi Arabia and personally interviewed using a pre-structured questionnaire. As an index of glycemic control, the glycated hemoglobin was assayed using a microcolumn technique. The main findings were: generally low score levels of knowledge, attitude and compliance. The mean glycated hemoglobin was significantly higher in type I (IDDM) (10.2 ± 2.2%) than in type 2 (NIDDM) diabetic respondents (9.1 ± 2.0%), $P = 0.001$. Evidence from this study suggests there is a need for sustained active patient education, support and evaluation, in order to increase patient involvement and self-reliance in the management of their diabetes. It is recommended that diabetes care be principally the responsibility of appropriately trained and culturally compatible members of the primary health care team working in partnership with other secondary care services. Medical audit of diabetes care at the primary health care level would improve clinical performance in this field.

Diabetes mellitus (DM) is a very common problem. It is estimated that there are 30 million diabetics worldwide [1]. It is a significant health problem in Saudi Arabia [2], with prevalence rates between 5% and 7% [3]. These rates are much higher than the 1.2% in the UK [4] but lower than the 35% among Pima Indians of Arizona [5]. It is suspected that diabetic patients find it difficult to comply with their treatment, especially when dietary measures are involved. This difficulty is reflected in their blood glucose level and body weight and may in the great part be due to the lack of appropriate perception of the disease and its management resulting in poor compliance and hence suboptimal glycemic control. Since optimal glycemic control reduces acute and chronic complications of diabetes [6], it is important that measures to improve diabetes care be adopted.

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There are many factors associated with the epidemiology of DM, such as obesity and genetic predisposition [4]. Bennett et al [4] studied the epidemiology of DM among Pima Indians and concluded that obesity may be a precipitating factor in the development of DM, but this can only be verified by long-term prospective incidence studies on the relationship between diabetes and obesity.

The objectives of this study were to explore in the participants the knowledge (K), the attitude to (A), and the compliance (P) in the management of their disease (KAP) and to study the relation between the KAP score and glycemic control (as measured by the glycated hemoglobin (GHB) and the body mass index (BMI)) in order to identify factors that may be of relevance in the planning of more effective diabetes education and treatment programs.

Levels of GHB reflect the time-averaged blood glucose levels that prevailed in the preceding six to eight weeks [7], the BMI is an index of obesity and an indirect indicator of glycemic control [8].

Patients and Methods

The current protocol at the Diabetes and Endocrine Centre (DEC) in Dammam, in the Eastern Province of Saudi Arabia, includes the following: GHB is measured every four months; screening for sickle cell disease and G-6-PD deficiency and other hemoglobinopathies, measurements of height and weight at first registration, and weight only thereafter.

The GHB was assayed by the cation-exchange chromatography method using a commercial kit GLYCO Hb QUIK COLUMN supplied by Helena Laboratories, Texas, USA. The chromatograms were developed according to the procedure proposed by the manufacturer.

Selection criteria included: Non-pregnant Saudi diabetic women aged 20 years or older with no hemoglobinopathies or G-6-PD deficiency. The files of all female patients attending the DEC were systematically randomly examined and 300 patients who met the inclusion criteria were included.

Insulin dependent diabetic patients (IDD) were defined as those with a deficiency of insulin who need insulin to prevent ketosis. Non-insulin-dependent diabetic patients (NIDD) were those with relative insufficiency of insulin who did not require insulin for the prevention of ketosis.

The study was preceded by a pilot study in which 30 participants of similar selection criteria were similarly selected and interviewed using the same questionnaire. Data from the 30 participants were excluded from the main study.

Patients were contacted and personally interviewed with the help of a prestructured questionnaire. Their weights and heights were then measured and 3 ml of venous blood samples collected into a labelled EDTA evacuated tube and refrigerated until the end of the session when it was transported to a nearby hospital laboratory for GHB assay.

The BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2) [9–12], and obesity was classified as mild (grade I), BMI 25 to < 30 kg/m^2; moderate (grade II), BMI 30 to 40 kg/m^2 and severe (grade III), BMI > 40 kg/m^2 [12].

The questionnaire consisted of questions on demographic data and personal and medical characteristics. In addition, the questionnaire contained fixed choice questions pertaining to the specific knowledge of the basic fundamentals of DM and certain aspects of management, statements consisting of a self-report of activities regarding the ability to follow dietary prescription and continuing adherence to daily caloric limit; the ability to use small amounts of food to avoid the hypoglycemic effect of insulin; reliability in insulin administration (or the use of hypoglycemic agents), enquiries into the importance of exercise, proper foot and skin care, urine and blood glucose home monitoring. Lastly, the questionnaire consisted of 13 statements that evaluated areas considered important for diabetes management such as the participant's satisfaction with the physician, her adjustment to DM [13–15] and the absence of major role disruption (inability to keep house, disrupted social relationship, etc.).

Reliability testing was carried out on 45 (15%) of the participants.

Coded data were entered into a personal computer using the Screen Primary Function for Personal Computer (SPF/PC) program [16] and analyzed with the Statistical Package for the Social Sciences (SPSS/PC+) [17].

Statistical methods employed were two independent samples and paired *t* tests, analysis of variance (ANOVA) followed by Duncan's multiple range test and multiple regression and correlation.

Results

Of the 300 diabetic Saudi women, 26% had IDDM and 74% NIDDM, with a mean age of 42.6 ± 9.1 years and 43.9 ± 9.0 years, respectively. Their age ranged from 20 to 65 years. The illiteracy rate was high at 81.7%. Only four were high school graduates. Seventy-four percent were married, 2% single, 6% divorced, and 18% were widowed.

A positive family history (FH) of DM was elicited in 68.3% of the participants, while 28% had none, and 3.7% did not know (Table 1). Significantly, more IDD (82.1%) gave a positive FM than NIDD participants (63.5%), $P < 0.001$. The reason for this is unclear.

The duration of DM ranged from 0.5 to 38 years, with a mean of 6.5 ± 4.9 years and was significantly longer among those with positive FH ($P < 0.001$) (Table 2).

Of the 78 IDD patients, 33.3% were administering the insulin themselves, 32.1% were given their injection by a relative, and 34.6% by the clinic nurse.

The overall knowledge score for the diet and nutrition components of the questionnaire was high: 95.7% of the participants had a score of $\geqslant$ 83.3%. Alarmingly, no respondent knew the effect of illness and infection on insulin dosage and therapy (Table 3).

The level of education correlated highly with the K score ($P < 0.001$). The K score ranged from 16 to 61 points with a possible maximum of 66 points, and a mean of 44.7 ± 7.7 points, with the IDD participants and those with positive FH scoring significantly higher than NIDD participants and those without a FH, $P = 0.002$ and $P < 0.001$, respectively.

The A score correlated negatively with the duration of DM ($P = 0.02$), but other factors such as the K score, age, age at onset of DM, parity, literacy level, and hospital stay did not affect the A score.

The P score correlated positively with the A score ($P = 0.04$), the K score ($P < 0.001$) and negatively with duration of DM ($P < 0.001$).

TABLE 1. *General characteristics of the 300 participants.*

Characteristics	Number	(Percent)
Marital status:		
Married	222	74.0
Single	6	2.0
Divorced	18	6.0
Widowed	54	18.0
Age groups in yrs:		
20–35	60	20.0
36–55	219	73.0
>55	21	7.0
Type of DM:		
I (IDD)	78	26.0
II (NIDD)	222	74.0
Family history of DM:		
Positive	205	68.3
Negative	84	28.0
Don't know	11	3.7

TABLE 2. *Test of significance between the variables by family history of DM.*

Description (mean)	Positive FH	Negative FH	*P* value
Age	42.8	45.1	0.05
Age at onset of DM	35.6	40.2	<0.001
Years of education*	1.3	0.6	0.01
Duration of DM	85.5	59.3	<0.001
No. of hospitalizations	0.5	0.2	0.02
Days in hospital	4.7	1.7	0.003

* Test of significance done by Mann-Whitney test.

TABLE 3. *Percentage distribution of answers to questions relating to certain aspects of diabetes care.*

Question	Number of correct answers	Percent
Effect of infection on insulin	0	0
Hypoglycemia management	249	83
Hypoglycemia prevention:		
Carrying sweets when out	29	9.7
Taking extra food prior to strenuous exercise	14	4.7
Home urine testing	5	1.7
Home blood glucose monitoring	3	1
Keeping a log diary	2	0.7
Foot care	84	28
Carrying DM I.D. card	3	1

ANOVA test of mean P score by marital status indicated a significant difference in mean P score between the four groups, with the married and single women scoring higher than divorced or widowed ($P = 0.01$).

The composite KAP score ranged from 56 to 130 points with a mean of 84 ± 11.6 and a possible maximum score of 156 points. The KAP score declined with advancing age ($P = 0.01$) and increased with the literacy level ($P = 0.002$) (Tables 3 and 4).

The BMI ranged from 18.8 to 62.7 kg/m^2, with a mean of 31.7 ± 5.9 kg/m^2. The overall obesity rate (BMI > 25 kg/m^2) was 89.7%, however, this rate is reduced to 57% when the index of obesity is taken as BMI $\geqslant 30$ kg/m^2 (Table 5).

The GHB assay is expressed as a percentage of total hemoglobin concentration, and ranged from 4.8% to 16.5%, with a mean of 9.4 ± 2.1%. There was a positive correlation between GHB and duration of DM ($P < 0.001$) and a negative correlation with the P and A scores, $P = 0.03$ and ($P = 0.01$), respectively.

IDD patients had a significantly higher GHB (10.2 ± 2.2%) than NIDD patients (9.2 ± 2.0%), $P = 0.001$. Furthermore, among IDD respondents, one-way ANOVA test for GHB by the mechanism of insulin administration, indicated a highly significant difference in mean GHB between self-injections (with the lowest GHB), and each of those injected by a relative or by a nurse ($P = 0.003$).

Discussion

The reasons for the high percentage of NIDD patients (89.2%) on oral hypoglycemic agents may be due to doctors either prescribing these agents prematurely without giving dietary measures enough time to be effective, or due to their giving in to patients' demands, or it may reflect a sample bias. In addition, the dominant presence of expatriate doctors and health personnel at the DEC exacerbated the socioculture barrier. This finding has implications for professional recruiting and training as well as for patient education.

The duration of DM was significantly longer in those with positive FH of DM ($P < 0.001$) and may be due to heightened awareness of diabetes leading to earlier diagnosis among those patients. Selective screening of those at risk is suggested.

The high mean GHB found may reflect suboptimal diabetes care. The significantly higher mean GHB in IDD patients is at variance with findings of other studies [18,19] and may reflect a difference in patient information and motivation, the severity of the disease, underdosage of insulin (for fear of hypoglycemia), or lack of optimal diabetes control in those subjects [8]. The higher GHB in IDD patients coupled with a significantly ($P = 0.002$) higher K score may testify to the existence of important gaps and inadequacies in their diabetes care.

Interestingly, within the IDD group of patients, those who administered the insulin themselves had a significantly lower GHB ($P = 0.003$) than those IDD patients who had to rely on a relative or a nurse for their insulin injection and may point to the difficulty they experience in compliance. This finding emphasizes the importance of training and encouraging diabetic patients to inject the insulin themselves. Such training should be individualized taking into consideration the various factors that have been shown to affect glycemic control.

There was a decline of KAP score with advancing age. This agrees with previous studies [20–22], with patients over 55 years having a lower score. This may be explained by the fact that those very patients were mostly illiterate. Older patients are

TABLE 4. *Distribution of KAP score by age groups in years.*

Performance (KAP) score (max. 156)	Age Groups in Years			
	20–35	36–55	>55	Total
>104	10	16	1	27
53–104	50	203	20	273
Total	60	219	21	300

TABLE 5. *Distribution of KAP score according to years of education.*

Performance (KAP) score (max. 156)	Years of Education				
	0	1–6	7–9	10–12	>12
>104	17	6	3	1	0
53–104	228	35	7	1	2
Total	245	41	10	2	2

at a greater risk, afflicted with multiple pathology and therapeutic regimens that would make them lose interest in their disease and in self-care.

Those patients with a positive FH of DM scored significantly higher than those without FH, ($P = 0.001$). This finding may be because the presence of a member of the family with DM increases awareness and the chances of discussion of DM at home [23,24].

The positive correlation of the P score with favorable A and K scores and hence better glycemic control reflect the need for continued patient education, long-term follow-up and support.

The high prevalence rate of obesity (89.7%) found in this study suggests that obesity is a significant problem among this diabetic population. It is possible obesity may have accelerated the phenotypic expression of diabetes in those who are genetically susceptible [5], but this can only be verified by prospective incidence studies on the relationship between obesity and diabetes. The high obesity rate detected in this and other Saudi studies [25–27] have shown considerable implications for the organization of preventive health care services in our community.

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PLASMA APOLIPOPROTEINS A-I, A-II, B, C-II, C-III, AND E LEVELS IN YOUNG KUWAITI MALE SURVIVORS OF MYOCARDIAL INFARCTION

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أجري تحليل لمستويات البلازما من الشحم والبروتين الشحمي وصميم البروتين الشحمي (A–I, A–II, C–II, C–III, E) لدى ١٨٠ مريضا من المرضى الصغار نسبيا والباقين على قيد الحياة بعد اصابتهم باحتشاء عضلة القلب (أعمارهم ٢٨ إلى ٤٥ سنة) ولدى ٢٠٠ شخص من الأصحاء والطبيعيين المطابقين من حيث الجنس والسن وذلك لتقييم أهمية تركيزات البروتينات الشحمية الصميمة بالمقارنة مع البروتينات الشحمية لدى مرضى احتشاء عضلة القلب. أظهر مرضى احتشاء عضلة القلب بالمقارنة مع الأصحاء زيادات ملحوظة لديهم في مستويات المركبات التالية: إجمالي الكولسترول، البروتينات الشحمية قليلة الكثافة، الكولسترول المرتبطة بالبروتينات الشحمية قليلة الكثافة (LDL) ، ثلاثي الغليسريد (TG) ، الكولسترول وثلاثيات الغليسريد قليلة الكثافة جدًّا (LDL–TG) ، الصميم ب، الصميم (C–III) الصميم E . لكن لم تلاحظ تغيرات ملموسة في مستويات الكولسترول عالي الكثافة (HDL3) والصميم (A–II) الصميم (C–II) لدى هؤلاء المرضى بالمقارنة مع الأصحاء. كانت مستويات البروتين الشحمي عالي الكثافة والكولسترول (HDL2) والصميم (A–I) منخفضة بصورة ملحوظة لدى مجموعة صغار المرضى الباقين على قيد الحياة بالمقارنة مع المجموعة المقابلة من الأصحاء. وأظهر تحليل وظيفة التمييز أن البروتينات الشحمية وصميمات البروتينات الشحمية الأكثر تمييزا لدى مرضى احتشاء عضلة القلب هي، بالترتيب التنازلي، كولسترول (HDL2) والصميم C–III ، والصميم B ، والصميم A–I وثلاثيات الغليسريد VLDL والكولسترول HDL . كما تدل النتائج على أن قياس الصميم C–III والصميم ب والصميم A–I بالاضافة إلى الكولسترول المرتبط بالبروتينات الشحمية عالية الكثافة HDL قد تكون له فائدة في التفريق بين الأصحاء الطبيعيين وبين مرضى احتشاء عضلة القلب.

Plasma levels of lipid, lipoprotein, and apolipoprotein (APO) A-I, A-II, C-II, C-III, and E were analyzed in 180 young survivors of myocardial infarction (MI) aged 28 to 45 years and in 200 sex-and age-matched normal healthy subjects to assess the importance of apolipoprotein concentrations in comparison with lipoproteins in MI patients. In comparison with control subjects, MI patients showed marked increases in the following parameters: total cholesterol (TC), low density lipoproteins (LDL) cholesterol, triglyceride (TG), very low density (VLDL) triglycerides, and cholesterol, and LDL-TG, apo B, apo C-III and apo E. There were no significant changes in levels of HDL_3 cholesterol, apo A-II and apo C-II in these patients compared with their controls. Levels of high density lipoprotein (HDL), HDL_2 cholesterol, and plasma apo A-I were markedly decreased in the young MI survivors' group when compared with their corresponding controls. Discriminant function analysis demonstrated that the better discriminating lipoproteins and apolipoproteins in MI patients in descending order were HDL_2 cholesterol, apo C-III, apo B, apo A-I, VLDL triglycerides and HDL cholesterol discriminated between patients and controls. Results indicate that measurement of apo C-III, B and A-I beside HDL_2 cholesterol were shown to be of potential use in differentiating normal controls from patients with MI.

Most studies of myocardial infarction survivors have shown that decreased cholesterol concentration in the high density lipoprotein (HDL) and/or HDL_2 cholesterol fractions and an increase in low density lipoproteins (LDL) fractions are risk markers in the development of coronary artery disease

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(CAD) [1,2]. The role of triglycerides in the development of CAD remains a subject of continuing controversy, but according to many studies, triglycerides are found to be one of the major risk factors for CAD [3–5]. On the other hand, serum apolipoproteins (apo) measurements are considered to be better discriminators than the levels of total or lipoprotein lipids [3,6–9]. Low levels of apo A-I (the major HDL protein) and high levels of apo B (the major LDL protein) were reported to be correlated positively to CAD [8,9]. Apo C-II and apo C-III (the major VLDL proteins have also been reported to play an important role in the catabolism of triglycerides and hence may contribute to CAD [10,11]. Apo C-II is an activator of lipoprotein lipase (LPL) which hydrolysates triglycerides while apo C-III reportedly inhibits LPL [12,13]. Apolipoprotein E (distributed equally in VLDL and HDL has also been implicated in the pathogenesis of CAD. It is important to know the effect of beta blockers on blood lipids when evaluating long-term success patients. A number of studies reported that beta blockers likewise elevate triglycerides and decrease HDL cholesterol. This is especially true for non-selective beta blockers without intrinsic sympathomimetic activity (ISA), such as propanolol [16]. However, it is not necessarily so for those with $Beta_1$ selectivity and ISA. Pindolol, a $Beta_2$ blocker with ISA, may actually decrease triglycerides and increase HDL cholesterol [17,18].

Our recent study [19] has shown moderately high levels of serum cholesterol and triglycerides among young male survivors of myocardial infarction below the age of 45 years. The present study was conducted to assess the importance of apolipoproteins: A-I, A-II, B, C-II, C-III, E measurements as risk factors for CAD in relation to the traditional quantitation of plasma and lipoprotein lipids in young Kuwaiti male survivors of MI.

Subjects and Methods

One hundred eighty Kuwaiti male patients, aged 28 to 45 years, who were admitted to the coronary care unit for a first myocardial infarction, were selected for this study. Diagnosis was based on clinical history, typical chest pain of thirty minutes duration or longer, electrocardiographic (ECG) signs of infarction and elevated serum concentration of enzymes including AST, ALT, CPK, CK-MB, and LDH. None of the patients were on medication prior to admission, and none had hypolipidemic therapy before or after infarction. Beta blockers used in this study were intrinsic sympathomimetic activity (e.g., exprenolol, trasicor, alprenolol) and the mean total daily dose required was 80 to 160 mg/day. Two hundred control subjects were selected from the university personnel and from patients seen at a medical outpatient clinic. All were comparable for age, height, body weight, and family history (Table 1). None had clinical or ECG evidence of CAD. Patients and controls had sedentary life styles and the majority smoked (over 92%). None of these patients participated in regular physical exercise and only 4% had a family history of MI. Patients were discharged from the hospital after about three weeks and were asked to return at two and four months following infarction.

Collection of Blood Samples and Analytical Methods

Blood samples were drawn after an overnight fast at 10, 60 and 120 day intervals after MI and sent immediately to the laboratory. The samples were centrifuged at 4° and 3000 rpm to separate the plasma (which was used for the immediate analysis of cholesterol, triglycerides and of apo A-I, A-II, B, C-II, C-III, and E). Ultracentrifugal fractionation of VLDL, LDL, total HDL, HLD_2 and HDL_3 fractions was performed sequentially.

Lipoprotein separation

Separation of lipoproteins was performed by a modified sequential ultracentrifugation method [20] in a preparative ultracentrifuge (Sorvall OTD 75.B, Biomedical Products Division, Washington, D.C., U.S.A.) using a fixed-angle rotor (type TFT 48.6) with appropriate adaptors. Plasma samples were centrifuged at $d = 1.006$ g/ml (40,000 rpm for 18 hours) and VLDL ($d < 1.006$ g/ml) was recovered as the top fraction. The bottom fraction was adjusted to $d = 1.006$-1.063 g/ml by NaCl and NaBr mixture (40,000 rpm at 15°C for 18 hours), and after ultracentrifugation, the top 2 ml was separated as LDL ($d < 1.063$ g/ml). The bottom fraction was HDL ($d = 1.063$-1.21 g/ml), HDL_2 and HDL_3 subfractions were separated, running total HDL fraction at $d = 1.063$-

1.125 g/ml (40,000 rpm at 15°C for 40 hours). After ultracentrifugation, HDL_2 ($d < 1.125$ g/ml) was recovered as the top fraction. The remaining bottom fraction was adjusted to $d = 1.125\text{-}1.21$ g/ml (40,000 rpm at 15°C for 48 hours), and HDL_3 ($d < 1.21$ g/ml) was recovered as the top fraction. The purity of the fractions was checked by electrophoresis using the Helena system (Helena Laboratories, Saint Leu, La Foret, France) and immunodiffusion techniques. In the Helena cellulose acetate electrophoresis system, VLDL appeared as a band in the prebeta-globulin region. LDL showed a band in the betaglobulin fraction. Total HDL banded in the alphaglobulin area, while HDL_2 and HDL_3 fractions showed two separate bands within the HDL region. Radial immunodiffusion plates with apo B and apo A-I antisera were used separately. Total HDL, HDL_2 and HDL_3 fractions showed precipitation rings only with apo A-I antiserum. LDL showed a strong precipitation ring with apo B antiserum but was negative for apo A-I. VLDL showed a much weaker precipitation ring than LDL with the apo B antiserum but showed a strong precipitation ring with apo C-III antiserum.

Lipid and Apolipoprotein Estimations

Plasma triglycerides [21], cholesterol [22], HDL, HDL_2, and HDL_3 cholesterol were analyzed in triplicate by Abbott Enzymatic Kits using an Abbott Super VP Analyzer (Abbott Diagnostic Products, GmbH, Wiesbaden, West Germany). Control plasma pools were supplied by Ortho Diagnostics Company and The Center for Disease (CDC, Atlanta, Georgia, USA). Control values were within the recommended range and between batch coefficients of variation were less than 1.8% and less than 4.5% for all the above estimations across the entire concentration range measured. Apolipoproteins A-I, A-II and B [23,24] values were determined by immunodiffusion (RID) assay. Plates were purchased from Immuno AG and samples were analyzed in duplicate including the standards and controls (Immuno AG, Vienna, Austria). Controls from CDC were also used and were found to be within the expected ranges. For apo A-I, inter-and intra-assay coefficient of variation was less than 3.5% at a level of 150 mg/dl and less than 4.5% at a level of 100 mg/dl. For apo A-II the coefficient of variation was less than 4.5% at a level of 70 mg/dl and less than 5.0% at a level of 40 mg/dl. For apo B it was less than 5.0% at a level of 100 mg/dl and less than 5.5% at a level of 70 mg/dl. Apolipoproteins C-II, C-III and E were determined by RID method [25] using plates purchased from Daiichi Pure Chemicals Company, Ltd., Tokyo, Japan. Inter-and intra-assay coefficient of variation was within the recommended range (below 10%). The method had the sensitivity of 46 to 82 mm^2 (diameter squared) per 5 mg/dl, 11 mg/dl and 6 mg/dl, apo C-II, C-III and E respectively, while the specificity was 80% to 120% of expected values for the three estimations.

Statistical Methods

Statistical significance for differences in lipoproteins and apolipoprotein compositions between groups was tested using one way analysis of variance and the two-tailed *t* test. The relationships between variables were calculated using Pearson correlation coefficients and linear regression analysis. Since strong intercorrelations were found between several lipoproteins and apolipoproteins, stepwise multiple discriminant analysis were performed to determine the sets of independent lipoprotein and apolipoprotein variables giving the best discrimination between patients and controls. The variable with the highest F value was entered at each step until no variable remained with a value (F to enter) of eight or more. All statistical tests were performed at the computer department of Kuwait Medical School using SPSS (Texas, USA) and BMDP6D [26] programs.

TABLE 1. *Clinical characteristics of MI survivors and control men.*

Variables	Controls (n = 200)	Patients (n = 180)
Age (yrs)	36.3 ± 6.0	35.8 ± 5.9
BMI (Kgm^2)	23.0 ± 1.5	22.8 ± 2.3
Systolic BP (mm Hg)	128.0 ± 2.6	136.0 ± 14.0
Diastolic BP (mm Hg)	75.0 ± 6.0	78.0 ± 8.0
Cigarette smoking (%)	95	94
Regular exercises	4.0	5.0
Family history of MI (%)	3.0	4.5

BMI = body mass index; BP = blood pressure; MI = myocardial infarction.

Results

Characteristics of MI Survivors and Controls

The mean age and Body Mass Index (BMI) for MI survivors were comparable to those of corresponding controls. No differences between the groups were observed with respect to blood pressure, level of regular exercise, smoking, family history of MI and lifestyles.

Lipoprotein Lipids and Apolipoprotein Concentrations in MI Survivors

The comparison between controls and MI survivors showed significantly elevated levels of total LDL and VLDL cholesterol, while triglycerides were elevated in plasma, VLDL, LDL and HDL fractions. In contrast, HDL and HDL$_2$ cholesterol levels were significantly decreased in the MI group compared to control subjects (Table 2).

Levels of apo A-I for MI survivors were significantly decreased while levels of apo B, apo C-III and apo E were significantly elevated in MI survivors compared to controls. There were no significant differences between apo A-II and apo C-II in MI survivors and controls (Table 3).

Effects of Beta Blockers on Plasma Lipid, Lipoprotein and Apolipoprotein Concentrations in MI Survivors

Comparison of plasma lipoprotein levels between MI survivors treated with beta blockers at 10, 60 and 120 days showed no significant differences for all parameters. Unlike lipids and lipoproteins, levels of apo A-I for MI at 120 days were significantly decreased when compared to 10 and 60 days after MI, while levels of apo B, C-III and E were significantly elevated (Table 4). However, a series of experiments were done on MI patients after 120 days to ensure the stability of the results.

Pearson Correlation Coefficients Between Lipids and Apolipoproteins in MI Survivors

Apolipoprotein A-I correlated positively with HDL cholesterol ($r = 0.41, P < 0.001$) and apo C-III ($r = 0.39$, $P < 0.001$) and negatively with VLDL triglycerides ($r = 0.50, P < 0.001$) and with apo B ($r = 0.50, P < 0.001$). A strong positive correlation between HDL and HDL$_2$ cholesterol ($r = 0.70$, $P < 0.0001$) were observed. Apo C-III correlated positively with VLDL triglycerides ($r = 0.39, P < 0.001$), apo E ($r = 0.70, P < 0.0001$) and apo B ($r = 0.46, P < 0.001$), while apo C-III correlated negatively with HDL cholesterol ($r = 0.30$, $P < 0.05$). Strong correlations were observed between apo C-II and apo C-III ($r = 0.70$, $P < 0.0001$). VLDL triglycerides were positively correlated to LDL cholesterol ($r = 0.30$, $P < 0.05$), triglycerides ($r = 0.81$, $P < 0.0001$), apo B ($r = 0.30$, $P < 0.05$), while negatively with HDL and HDL$_2$ cholesterol ($r = 0.30$, $P < 0.05$ for both).

TABLE 2. *Concentrations of plasma and lipoprotein lipids in MI survivors and control men.*

	Controls (n = 200)	MI survivors (n = 180)	*P* value[a]
Cholesterol			
Total	5.20 ± 0.68	6.08 ± 1.06	< 0.0001
VLDL	0.76 ± 0.28	0.98 ± 0.32	< 0.0001
LDL	3.02 ± 0.56	4.10 ± 0.85	< 0.0001
HDL	1.33 ± 0.16	1.01 ± 0.07	< 0.0001
HDL$_2$	0.59 ± 0.07	0.30 ± 0.11	< 0.0001
HDL$_3$	0.74 ± 0.07	0.73 ± 0.076	NS
Triglycerides			
Total	1.28 ± 0.46	2.27 ± 0.55	< 0.0001
VLDL	0.85 ± 0.42	1.64 ± 0.36	< 0.0001
LDL	0.31 ± 0.09	0.45 ± 0.093	< 0.0001
HDL	0.19 ± 0.095	0.23 ± 0.09	< 0.0001

a = MI survivors compared to controls; NS = not significant. Results are mean ± SD in mmol/L.

Values are mean ± SD. Lipoprotein densities: VLDL, d < 1.006 gm/ml; LDL d = 1.006–1.063 g/ml; HDL$_2$, d = 1.063–1.125 g/ml; HDL$_3$, d = 1.125–1.21 g/ml.

TABLE 3. *Plasma apolipoprotein concentrations in MI survivors and control men.*

	Controls (n = 200)	MI survivors (n = 180)	*P* value[a]
Plasma:			
Apo A–I	148.9 ± 18.1	117.8 ± 11.7	< 0.0001
Apo A–II	39.7 ± 5.7	38.8 ± 4.3	NS
Apo B	100.5 ± 15.0	131.5 ± 13.4	< 0.0001
Apo C–II	3.2 ± 0.1	3.4 ± 0.1	NS
Apo C–III	6.5 ± 0.1	10.5 ± 0.1	< 0.0001
Apo E	3.4 ± 0.25	3.8 ± 0.46	< 0.001

Results are means ± SD in milligrams per deciliter; NS = not significant; Apo = apolipoprotein. Values are mean ± SD. a = MI survivors compared to controls.

Stepwise Discriminant Analysis Between Controls and MI Survivors at Four Months For Lipid, Lipoprotein and Apolipoprotein Variables

Stepwise discriminant analysis was performed to determine which variables were most important in differentiating between controls and MI patients (Table 5). These variables were used to compute scores for the likelihood of individuals belonging to the patient and control groups. In every analysis serum HDL$_2$ cholesterol was always the most discriminating variable. Other variables that significantly improved discrimination were apo C-III, apo B, apo A-I, VLDL triglycerides, and HDL cholesterol. The inclusion of other lipoprotein or lipid levels did not change the discrimination provided by HDL cholesterol, apo C-III, apo B, and apo A-I. Specificity and sensitivity referred to the percentage of the maximum error expected in the sample groups, and therefore reflected the percent correctly classified between the control (specificity) groups and the patient (sensitivity) groups.

Discussion

The significant elevation of cholesterol, LDL (the major cholesterol carrying lipoprotein), triglycerides, VLDL (the major triglyceride carrying lipoprotein) and the low levels of HDL and HDL$_2$ cholesterol, but not HDL$_3$ cholesterol in young MI survivors, i.e., Kuwaiti males, was in agreement with some of the previously reported data in young males with MI [6,7,14,27,28–31]. Conversely, the observed high levels of apo B and low levels of apo A-I and their correlations with other lipids and lipoproteins in MI patient group may reflect the increased production and/or impaired catabolism of VLDL-LDL particles and may suggest a possible metabolic and functional association among them [30,32–36].

TABLE 4. *Effect of beta blockers on plasma lipid, lipoprotein, and apolipoprotein levels in MI survivors.*

	MI survivors			
	10 days	60 days	120 days	*P* value^a
HDL–C	1.00 ± 1.08	1.02 ± 0.10	1.01 ± 0.01	NS
T–TG	2.24 ± 0.60	2.26 ± 0.66	2.27 ± 0.55	NS
Apo A–I	128 ± 12.0	124 ± 11	117.8 ± 11.7	0.001
Apo B	121 ± 14	126 ± 15	131.5 ± 13.5	0.0001
Apo C–III	9.5 ± 0.09	9.6 ± 0.11	10.5 ± 0.10	0.05
Apo E	3.6 ± 0.43	3.7 ± 0.44	3.8 ± 0.46	0.05

Results are meanf± SD in millimole per liter. *For HDL–C, T–TA and milligrams per deciliter for apolipoproteins.
^{a} = 120 day MI survivors compared to 10 day MI survivors. T = total; C = cholesterol; TG = triglycerides; APO = apolipoproteins.

TABLE 5. *Stepwise discriminant analysis between controls and MI survivors for lipoprotein and apolipoprotein variables.*

Significant variables	Classification function coefficients			Percent correctly classified		
	Controls	Patients	F	Controls (specificity)	Case (sensitivity)	Total
HDL$_2$–C	35.75	13.16	69.20	98%	97%	97.75%
Apo C–III	24.94	33.41	54.10			
Apo B	0.69	0.85	18.01			
Apo A–I	0.72	0.68	16.50			
HDL–C	32.50	13.00	15.00			
VLDL–TG	5.72	10.61	13.05			
T–TG	6.01	8.61	12.60			

Stepwise discriminant analysis is a form of multivariate analysis. The discriminant function selects from a set of variables those significantly ($P < 0.001$) classifying cases and controls as indicated by an F value above 8 and lists these variables in descending order of significance. C = cholesterol; apo = apolipoprotein; TG = triglyceride; T = total serum.

In agreement with our earlier study and other studies [19], lipids and lipoproteins do not change for 120 days after infarction. However, in the present study apolipoproteins, A-I, B, C-III and E showed a sharp change between 10 days and 120 days, but remained stable after that. The reason for these changes is not clear, but could be due to different genetic and/or environmental influence, diet, exercise, infarction size or beta blockers [8,18,19]. Beta blockers used in this study had no clear effects on lipoprotein levels [17,18]. Previous studies have shown that apo C-III level is associated with the triglyceride level [11,13]. In this study, the increase in total and VLDL triglyceride was accompanied by the increase in apo C-III but not apo C-II. Furthermore, our finding of high apo B and apo E and of lower apo A-I and their correlations to apo C-III [2,7,24] may have added information to the relationship of apo C-III on the lipid imbalance in MI patients in that apo C-III level probably reflects an independent risk factor.

Regarding apo C-II level, we did not find any significant difference between MI group and the control subjects, which may suggest that apo C-III plays a role in regulating LPL by exerting an inhibitory effect in contrast to apo C-II, and therefore, increases in total and VLDL triglyceride levels in these patients [11,13].

The stepwise discriminant analysis which we applied in this study may have allowed us to sort out the best discriminator factors between the MI group and the control subjects. Previous studies on MI survivors indicated that apo B and A-I are as effective discriminators as are cholesterol triglycerides, HDL and HDL_2 cholesterol [36–38]. In our study, HDL_2 cholesterol proved to be the best discriminator in the young MI patients followed by apo C-III, apo B, apo A-I, VLDL triglycerides and HDL cholesterol. Furthermore, HDL_2 cholesterol, apo C-III, B, A-I provided a discriminant score that could not be changed by addition of any other lipoproteins or lipids measured. The percentage of correctly classified subjects was 98% and 93% for controls and MI patients. Thus, apolipoproteins measurement, particularly apo C-III, may be useful in predicting and preventing CAD [37,38].

Thus, the current evidence re-emphasizes the importance of HDL_2 cholesterol, apo B, and apo A-I as more useful indicators in assessing CAD risk than triglycerides, cholesterol and HDL cholesterol.

These results also indicate that the addition of the serum apo C-III determination to the lipid profile may be of clinical use in early identification of coronary risk. Finally, it appears that measurements of either apolipoproteins or lipids independently, or in combination would show a stronger relationship to CAD in young patients. However, more extensive prospective studies must be organized before it can be recommended that apolipoprotein measurements completely replace lipoprotein lipids.

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PATTERN OF PRIMARY GASTROINTESTINAL TRACT CANCER IN THE SOUTHERN PROVINCE

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شخصت في مختبر التشريح المرضي في مستشفى عسير المركزي خلال السنوات الأربع، ١٩٨٧ ـ ١٩٩٠م مائتان وأربع وثلاثون حالة ورم أولي في السبيل المعوي. هذه دراسة تحليلية لهذه الحالات من حيث ترتيب الدرجات والتوزيع حسب الجنسية والسن والجنس ومواقع الإصابة الأولية والنمط النسيجي المرضي. شكل السعوديون نسبة ٨٨٪ من الحالات وكانت نسبة غير السعوديين ١٢٪. كان متوسط عمر المرضى ٦٠ ± ١٢ سنة ونسبة الذكور إلى الإناث ٢ : ١. كان سرطان الكبد الأولي أكثر الأورام تواردا (٢٩٪) تلاه سرطان المعدة (٢٧٪) ثم سرطان القولون والمستقيم ٢١٪ فسرطان المريء ١٣٪. قارنّا مشاهداتنا بمثيلاتها في مناطق أخرى من المملكة.

Two hundred thirty-four cases of primary gastrointestinal tract malignancy were diagnosed at the histopathology laboratory of Asir Central Hospital over a four-year period, from 1987 to 1990. The current study is a retrospective analysis of these cases regarding rank orders, distribution according to nationality, age and sex, primary sites affected and the histopathologic pattern. Eighty-eight percent of our cases were Saudi and 12% were non-Saudi nationals. The mean age of patients was 60 ± 16 years with a male:female ratio of 2:1. Primary liver cancer was the most common malignancy (29%), followed by gastric cancer (27%), colorectal cancer (21%) and esophageal cancer (13%). Comparison of our findings to those from other provinces of the Kingdom are also included.

The gastrointestinal tract and its accessory glands, namely liver, pancreas and gallbladder constitute one of the most frequently affected system by cancer in the human body. In Western countries gastrointestinal tract cancer is among the leading causes of mortality [1,2]. In South East Asia and Africa the gastrointestinal tract ranks as the number one site affected by cancer [1,2]. Several environmental factors, dietary habits, smoking, alcohol and precancerous conditions have been linked to the development of gastrointestinal tract cancer [3–6]. Therefore, studying the pattern of gastrointestinal tract cancer at a certain location in the world might help health services to detect population groups at high-risk of developing cancer and to reduce the number of patients affected by this disease. This task could be approached by eliminating hazardous environmental factors, modifying dietary habits and screening high-risk population for precancerous conditions and/or early cancer.

Several reports from various provinces of the Kingdom of Saudi Arabia studying the pattern of alimentary tract cancer, have been documented in the medical literature during the last few years [7–10]. Our current report is the first to describe this pattern in the Southern Province of the Kingdom. However, a recent report from this hospital [11], has studied the general pattern of cancer in this province where gastrointestinal tract cancer ranked second, followed by skin cancer. The current study aims at further analysis of primary gastrointestinal tract malignancy in this region of the Kingdom and to compare this pattern with those recently reported from other provinces of the country.

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Material and Methods

The histopathology laboratory at Asir Central Hospital, located in Abha, receives specimens from the city of Abha as well as general hospitals located in Khamis Musayt, Bish, Muhayl, Sarat Aubida, Zahran Al-Janoub, Ahad Rufidah and Rijal Alma. Geographic and demographic descriptions of this region of the Kingdom have been included in a recent report from this hospital [11]. The histopathologic reports of 234 cases of primary gastrointestinal tract malignancy diagnosed over a four-year period (1987 to 1990) were reviewed. The patients' charts were reviewed only when the data in the request forms were inadequate. Only one specimen per patient was included even though the patient might have had more than one specimen. Whenever the same patient had a biopsy and a resection specimen our data were obtained from the latter report.

All the specimens were fixed in formalin and hematoxylin-eosin stained sections were examined. Special stains were done in cases of poorly differentiated neoplasms to reach a definitive diagnosis. The data were collected, tabulated and our results are presented as percentage (crude relative) frequencies and/or absolute numbers.

Results

Table 1 shows the distribution pattern of primary gastrointestinal tract malignancy in seven locations among Saudi, non-Saudi and the total population. Primary liver cancer ranks number one in our population followed by gastric, colorectal and esophageal cancer. This ranking order is comparable among Saudi and non-Saudi patients in six locations. Primary liver cancer exhibited significant difference among the two populations where 31% of Saudi patients were affected compared to only 10% of non-Saudis.

The mean age of the population studied was 60 ± 16 years (SD), with a male:female ratio of approximately 2:1 (158 males and 76 females). This male:female ratio of 2:1 to 3:1 was seen in hepatic, gastric, esophageal, and small intestinal cancer whereas this ratio was approximately 1:1 in colorectal cancer (26 males and 25 females). In pancreatic and gallbladder cancer this ratio was reversed to be 1:8 and 2:3, respectively (Table 2).

TABLE 1. *Distribution of 234 cases of primary gastrointestinal tract malignancy according to primary site and patients' nationality.*

Location	Saudi cases (%)	Non-Saudi cases (%)	Total population cases (%)
Liver	64 (32)	3 (10)	67 (29)
Stomach	52 (25)	11 (38)	63 (27)
Colorectal	42 (21)	8 (28)	50 (21)
Esophagus	28 (14)	3 (10)	31 (13)
Pancreas	7 (3.5)	2 (7)	9 (4)
Small intestine	7 (3.5)	2 (7)	9 (4)
Gallbladder	5 (2)	–	5 (2)
Total	205	29	234

TABLE 2. *Distribution of 234 cases of primary gastrointestinal tract cancer according to age and sex.*

Location	Age mean ± SD	Sex Male (%)	 Female (%)	Total
Liver	62 ± 18	53 (79)	14 (21)	67
Stomach	60 ± 15	50 (79)	13 (21)	63
Colorectal	57 ± 14	26 (52)	24 (48)	50
Esophagus	65 ± 12	20 (65)	11 (35)	31
Pancreas	54 ± 15	1 (11)	8 (89)	9
Small intestine	36 ± 20	6 (67)	3 (23)	9
Gallbladder	60 ± 8	2 (40)	3 (60)	5
Total	60 ± 16	158 (68)	76 (32)	234

Table 3 shows further analysis of age distribution of the seven locations of primary gastrointestinal tract cancer. Seventy percent of our cases belonged to age groups of > 55 years of age (168 cases). Small intestinal cancer occurred among younger age groups where seven of the nine cases were patients less than 45 years of age.

The distribution of esophageal, gastric and colorectal cancer along the gastrointestinal tract proper is illustrated in Table 4. The majority of esophageal cancer occurred in the lower one third of the esophagus (71%) followed by the middle one third (20%) and the upper one third (9%). Gastric cancer was equally located in the antrum (41%) and the body of the stomach (40%) followed by the fundus (19%). The rectosigmoid segment was affected in 56% of all cases of colorectal malignancy, cecum (22%) and the remaining colorectal tract (22%).

Histologically, 197 cases were adenocarcinoma including hepatocellular carcinoma, 19 cases were

TABLE 3. *Distribution of 234 cases of primary gastrointestinal tract cancer among various age groups.*

	Age (years)								
Location	1–12	13–24	25–34	35–44	45–54	55–65	66–75	>76	Total
Liver	2	–	–	1	11	18	23	12	67
Stomach	–	1	4	3	12	20	18	5	63
Colorectal	–	1	2	2	11	18	11	5	50
Esophagus	–	–	2	–	1	11	13	4	31
Pancreas	–	–	1	2	2	1	3	–	9
Small intestine	2	–	–	5	–	1	1	–	9
Gallbladder	–	–	–	–	1	3	1	–	5
Total	4	2	9	13	38	72	70	26	234

TABLE 4. *Locations of esophageal, gastric and colorectal cancer along the gastrointestinal tract proper in 144 cases.*

Organ	Location	No(%)
Esophagus	Upper one third	3 (9)
	Middle one third	6 (20)
	Lower one third	22 (71)
Total		31
Stomach	Fundus	12 (19)
	Body	25 (40)
	Antrum	26 (41)
Total		63
Colorectal	Cecum	11 (22)
	Ascending colon	2 (4)
	Hepatic flexure	1 (2)
	Transverse colon	2 (4)
	Splenic flexure	3 (6)
	Descending colon	3 (6)
	Sigmoid colon	9 (18)
	Rectum	19 (38)
Total		50

squamous cell carcinoma, 17 cases were non-Hodgkin's malignant lymphoma and one case of leiomyosarcoma of the small intestine. All cases of squamous cell carcinoma were located in the esophagus (three cases in the upper one third, five cases in the middle one third, and 11 cases in the lower one third). Nine cases of non-Hodgkin's malignant lymphoma were located in the stomach, four cases in the small intestine, three cases in the colorectal tract and one case in the head of the pancreas. Sixty-two cases of primary liver malignancy were hepatocellular carcinoma, three cases where cholangiocarcinoma and two cases were hepatoblastoma.

Discussion

Patterns of primary gastrointestinal tract malignancy in five studies from three provinces of the Kingdom of Saudi Arabia are summarized in Table 5 [7–10]. All five studies agree that the colorectal segment is not the most common site of origin of primary gastrointestinal tract cancer in Saudi Arabia. The latter ranked third in three studies [7,9] and second [8] and fourth [10] in the remaining two reports. Primary liver cancer is the most common type of cancer included in our study in agreement with the report from the Riyadh Armed Forces Hospital (RAFH) [9]. Primary liver cancer was not high ranking among patients from the Eastern Province of the Kingdom [8] (13% compared to 20%, 27%, 29%, and 35% from other locations).

Gastric cancer patients presented in 27% of our patients which is comparable to the reports from Riyadh Central Hospital (RCH) (31%) [10] and Dhahran Health Center (DCH) (30%) [8]. These figures are higher than the figures reported from King Faisal Specialist Hospital and Research Centre (KFSH&RC) (14%) [7] and the RAFH in Riyadh (15%) [9]. Colorectal cancer presented in 21% of our cases, a figure slightly lower than the figure reported from the DHC (23%) [8] and slightly higher than figures reported from three Riyadh hospitals (18%, 18%, and 19%) [7,9.10].

Our results agree with figures from the DHC [8] that esophageal cancer is not high ranking among various primary gastrointestinal tract cancer. Esophageal cancer presented in 13% of our patients and in 15% of patients from the Eastern Province [8]. These figures are lower than three

TABLE 5. *Patterns of primary gastrointestinal tract cancer in five studies from different provinces of the Kingdom of Saudi Arabia.*

Location	Asir Central Hospital	Riyadh Central Hospital	Dhahran Health Center	KFSH&RC* Riyadh	Armed Forces Hospital, Riyadh
Liver	29% (1)	20% (2)	13% (5)	27% (2)	35% (1)
Stomach	27% (2)	31% (1)	30% (1)	14% (4)	15% (4)
Colorectal	21% (3)	18% (4)	23% (2)	18% (3)	19% (3)
Esophagus	13% (4)	19% (3)	15% (3)	32% (1)	22% (2)
Pancreas	4% (6)	3% (6)	15% (4)	5% (5)	6% (5)
Small intestine	4% (5)	3% (5)	NA	NA	NA
Gallbladder	2% (7)	4% (7)	4% (6)	4% (6)	3% (6)
Total number of cases	234	377	108	561	383

Figures in % are: percentage (crude relative) frequencies.
Figures in parentheses are rank orders.
*KFSH&RC = King Faisal Specialist Hospital and Research Centre. NA = not available.

reports from Riyadh where esophageal cancer presented in 32% of cases reported from KFSH&RC [7], 22% of cases reported by the RAFH [9] and 19% of patients from RCH [10]. Eleven out of 22 cancer cases of the lower one third of the esophagus were adenocarcinomas and the remaining 11 cases were squamous cell carcinomas. In the cardiac region, separation of primary esophageal adenocarcinoma from a gastric primary is frequently impossible. In the current study, neoplasms located mainly on the esophageal side of the gastroesophageal junction were considered as primary tumors of the lower one third of the esophagus. The locations of the neoplasms were assessed either during endoscopy or in resected specimens. Our results regarding pancreatic cancer agrees with results from three hospitals located in Riyadh where this type of cancer was not common, representing 3%, 4%, 5%, and 6% of the four studies [7,9,10]. These figures are significantly low when compared with the figure of 15% reported from the Eastern Province [8].

Our results also agree with other reports regarding age and sex distribution of primary gastrointestinal tract cancer except for the unexpected yet interesting finding that pancreatic cancer in this region of the Kingdom is more common among female patients (male:female ratio 1:8). This finding is also different when compared to the distribution of this type of cancer among patients from Western countries where the male:female is at least 1.5:1 [12]. A histopathologic finding of interest in the current study is the presence of nine cases of non-Hodgkin's malignant lymphoma out of 63 cases of gastric cancer, accounting for 14% of all patients with stomach malignancy. This figure is higher than other reports from the Kingdom where malignant lymphoma presented only 2% of all patients with gastric malignancy [10]. However, the distribution of malignant lymphoma in the small intestine and colorectal segment are comparable to findings from other provinces [10]. Also, the distribution pattern of malignancy along the esophagus, stomach and colon in our study is comparable to reports from other provinces of the Kingdom and Western countries where the lower one third of the esophagus, antrum and rectosigmoid region are the most commonly affected sites.

The current study supports previous findings that the upper gastrointestinal tract segment is more commonly affected by cancer when compared to the colorectal segment and that primary liver cancer is one of the major types of malignancy affecting the gastrointestinal tract among patients from Saudi Arabia. This pattern of malignancy has also been reported from southeast Asia and Africa, yet, different when compared to the pattern seen in western Europe and the United States. The colorectal segment accounts for more than 75% of primary gastrointestinal tract cancer in Western countries [2] and the already low incidence of upper gastrointestinal tract cancer in these countries is declining even more according to recent reports [13]. All non-Saudi patients included in our study are of Middle Eastern nationalities and they presented with a high incidence of gastric cancer (38%) which might indicate that the pattern of primary gastrointestinal tract cancer in Saudi Arabia is also true in other Middle Eastern countries. Differences in the pattern of gastrointestinal tract cancer in various reports from Saudi Arabia could be partially attributed to the selectivity of the patients included. Reports from RAFH [9], KFSH&RC [7] in Riyadh included selected cases referred for advanced treatment whereas our cases and those from RCH [10] and DHC [8] represent a general hospital population, therefore providing a better picture of the actual pattern of malignancy.

Except for the fact that the high incidence of hepatitis B virus antigenemia explains the pattern of primary liver cancer in our study, the explanation for the pattern of gastric, esophageal and colorectal cancer is still an enigma. Further studies of the dietary habits, smoking, environmental factors and the incidence of precancerous gastric and esophageal lesions will be essential to have a better understanding of the current pattern of primary gastrointestinal tract malignancy in the Kingdom of Saudi Arabia.

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SQUAMOUS CELL CARCINOMA OF THE ANAL REGION AT THE KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

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تسجل هذه الدراسة النواحي الوبائية لسرطان الخلايا الحرشفية في الشرج والقناة الشرجية كما ظهرت لمستشفى الملك فيصل التخصصي ومركز الأبحاث. أجريت الدراسة على ثمانية وثلاثين (٣٣ سعوديا) مريضا، ٢٤ من الذكور و ١٤ من الإناث. وكانت أعمارهم تتراوح بين ٣٢ و ١٠٠عام. كان أربعة وعشرون مريضا مصابين بأورام في القناة الشرجية واثنا عشر كانوا مصابين بسرطان الهامش الشرجي. كان معظم المرضى من الرياض أو المنطقة الشرقية أو المدينة المنورة. وقد حضر أغلبهم بشكوى وجود نزف أو كتل أو ألم. وتراوحت مدة الأعراض لديهم من شهر واحد إلى أكثر من سنتين. عانى أربعة عشر من المرضى من مشكلات شرجية في الماضي. كان توزيع الآفات متساويا تقريبا بين النصفين الأمامي والخلفي للشرج. كانت العقد الاربية لدى تسعة عشر مريضا طبيعية من الناحية السريرية، وثلاثون كانوا يعانون من سرطان حرشفي الخلايا (ورم بشروي)، وثمانية منهم وجدت لديهم أورام مذرقية المنشأ أو قاعية المنشأ. وكانت معظم الأورام متوسطة أو ضعيفة التمايز. ثمانية وعشرون مريضا كانوا مصابين بأورام من الفئة الأولى أو الثانية. خمسة من المرضى كانت لديهم دلائل على وجود انتقالات منذ المراجعة الأولى. عولج ثمانية مرضى باجراء استئصال جزئي للمستقيم من خلال البطن والعجان. أجريت عملية تحويل لفتحة القولون لستة من المرضى. عولج خمسة عشر مريضا بالأشعة فقط، وعولج ثلاثة بالعلاج الكيميائي وحده. كما عولج أربعة عشر مريضا بالأشعة فقط، وعولج ثلاثة بالعلاج لكيميائي وحده. كما عولج أربعة عشر مريضا بالعلاج الكيميائي والشعاعي معا. كان عدد الذكور الذين أصيبوا بأورام في كل من القناة الشرجية والهامش الشرجي أكبر بعشر سنوات. وكان عدد المصابين بأورام القناة الشرجية ضعف عدد المصابين بأورام الهامش الشرجي. وكانت العقد الإيجابية أكثر لدى المرضى الذين يعانون من أورام الهامش الشرجي. وكانت أورام القناة الشرجية أقل تمايزا. وكانت المتابعة غير كافية.

This study documents the epidemiological aspects of squamous cell carcinoma of the anus and anal canal as it has presented to the King Faisal Specialist Hospital and Research Centre (KFSH&RC). Thirty-eight (33 Saudis) patients, 24 males and 14 females were studied. They ranged in age from 32 to 100 years. Twenty-four had anal canal tumors and 12 had anal margin cancers. Riyadh, the Eastern Province or Medina provided most patients and the majority presented with bleeding, a lump or pain. Symptom duration ranged from one month to more than two years. Fourteen had previous anal problems. There was an almost equal distribution of lesions between the anterior and posterior halves of the anus. Nineteen had clinically normal inguinal nodes. Thirty had squamous cell carcinoma (epidermoid) and eight had cloacogenic/basiloid tumors. Most tumors were either moderately or poorly differentiated. Twenty-eight presented with T_3 or T_4 tumors and only ten presented with T_1 or T_2 tumors. Five had evidence of metastases at initial presentation. Eight were treated by abdominoperinal resection of the rectum. A diversion colostomy was performed in six. Fifteen received radiotherapy alone but only three were treated by chemotherapy alone. Combination chemotherapy and radiotherapy was given to 14. More males than females had both anal canal and anal margin tumors. Patients with anal margin tumors were on average ten years older. There were twice as many with anal canal as anal margin tumors. There were more node-positive patients with anal margin tumors. Anal canal tumors were less well-differentiated. Follow-up was inadequate.

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Recently, there has been a renewed general interest and a gradual increase in the incidence of squamous cell carcinoma of the anus and anal canal (SCCA) in homosexual and anoreceptive bisexual males. Squamous cell carcinoma of the anus and anal canal is nevertheless an uncommon disease and only a few large series have been reported. SCCA represents only 3% to 5% of all anorectal malignancy [1]. For biological and therapeutical reasons, squamous cell carcinoma of the perianal area (anus) and squamous cell carcinoma occupying the anal canal are considered separately [1,2]. Squamous cell tumors of the perianal region seem to metastasize to regional lymph nodes more often than those of the anal canal [1].

Treatment of SCCA is still controversial [3,4]. Surgery alone is not adequate. Radiotherapy seems to be effective in the eradication of the disease since the tumor is quite radiosensitive. Nigro and others [5,6], however, have supported a multimodality approach for the treatment of the SCCA employing radiotherapy and chemotherapy (5-fluorouracil and mitomycin C) and superior long-term results are claimed for the "Nigro" technique.

The Kingdom of Saudi Arabia (KSA) does not have a national cancer registry. The King Faisal Specialist Hospital and Research Centre (KFSH&RC) has, however, maintained its own cancer registry since it first admitted patients in 1975. How well this registry reflects the true state of neoplasia within the Kingdom remains uncertain. While most of many histological types of tumors are referred to the hospital, the exact numbers of patients being treated "elsewhere" are unknown. KFSH&RC registry data is thus subject to bias (referral) and since total population data are not available within the Kingdom, the true incidence rates per 100,000 population for any tumor can not be calculated.

The data used in this report are based on KFSH&RC files and are subject to the above constraints. Alternative and better epidemiological data regarding SCCA in the Kingdom do not exist.

This study was undertaken to document some of the epidemiological aspects of the disease as it has presented to the KFSH&RC and to see how it has been treated in our hospital.

Material and Methods

A modification of the TNM-IUCC system of staging tumors has been used at the KFSH&RC (Table 1) [7]. All cases of SCCA referred to KFSH&RC between June 1975 and December 1990 have been reviewed retrospectively. Information concerning each patient was obtained from the cancer registry and entered onto a predesigned proforma. Individual patient charts were also examined. The collected data was analyzed by personal computer using a data analysis software program written by one of the authors (WHI). As explained in the introduction, we do not claim that our data base represents all cases of SCCA in the Kingdom. We were able to review a total of 39 charts with a diagnosis of "SCCA", and these patients comprise the data set for this study. It is believed that this study represents the first series of SCCA reported in the Kingdom.

Follow-up data for these patients was inadequate because most patients were from outside of the Riyadh area and most patients either returned to their referring physician or simply declined follow-up.

Results

Thirty-nine patients with "SCCA" were studied. One patient was found on histological examination to have a malignant melanoma and was excluded from further study leaving 38 patients for analysis. There were 24 males and 14 females; 33 Saudis, one American, one Lebanese, two Yemenis, and one Filipino. The patients ranged in age from 32 to 100 years. The mean age for males was 55.7 years and for females 58.7 years. Twenty-four patients had anal canal tumors and 12 patients anal margin cancers (63.2% and 31.6%). In two patients the tumor site was unknown. Of the 33 Saudis, most came from Riyadh, the Eastern Province or Medina (9, 7, and 5) and three each from Gizan, Asir and Makkah (Figure 1). Most of the patients presented with the triad of bleeding, a lump and pain. Fourteen patients (36.8%) presented with bleeding as their main complaint. Another 11 found a lump and seven patients presented with a history of pain. The duration of symptoms ranged from one month to more than two years (Table 2). Eighteen patients presented within the first three months of developing symptoms but eight patients presented having had symptoms for longer than a year. Fourteen patients gave a history of previous anal problems; i.e., piles, fissure, pruritis and fistula (36.8% of all patients). Seven patients presented with a history of piles and four patients had had a previous fistula in ano.

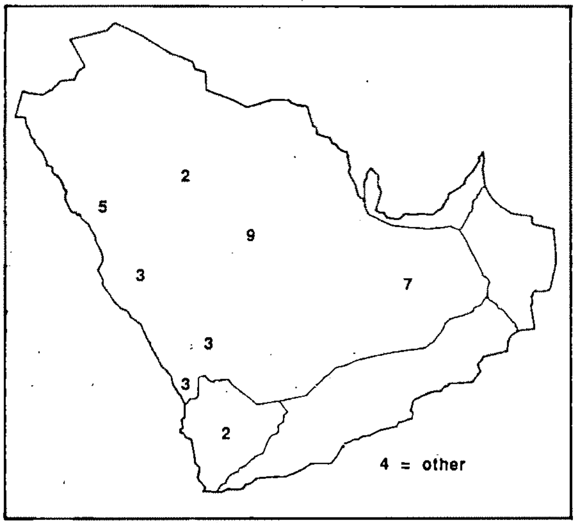

FIGURE 1. Distribution of cases of SCCA by geographic region.

TABLE 1. *SCCA: definition of T–stage [Papillion, 1982].*

T–stage	Definition
T_1	<2 cm
T_2	2 cm–<5 cm
T_3	>5 cm
T_{4a}	invading vaginal mucosa
T_{4b}	invading neighboring structures
T_5	insufficient information available

TABLE 2. *Duration of symptoms.*

Duration	Number
<1 month	2
1–2 months	7
2–3 months	9
3–6 months	3
6–12 months	5
1–2 years	5
>2 years	3
unknown	4

There was an almost equal distribution of lesions between the anterior and posterior halves of the anus and there were three patients who presented with circumferential lesions. Nineteen patients (50%) had clinically normal inguinal nodes. Eleven of 12 patients examined (92%) were found to be histologically positive and one was negative although thought to be positive on clinical grounds. Six patients' nodes were not biopsied. Thirty patients were histologically found to have a pure squamous cell carcinoma (epidermoid) (Table 3) and eight patients had a cloacogenic/basiloid tumor. Most patients had either moderately or poorly differentiated tumors. Twenty-eight patients (73.7%) presented with either T_3 or T_4 tumors. Only ten patients (26.3%) presented with T_1 or T_2 tumors. Five patients had evidence of non-nodal metastases at initial presentation (13.2%). Metastases were shown by abdominal CT scan in three patients and by skeletal scan in two patients. Metastases were present in the liver in one patient, the bladder in two patients and the ribs and clavicle of the two remaining patients.

Many modalities of treatment were used (Tables 4 and 5); surgery, radiotherapy, or chemotherapy alone or a combination of chemotherapy and radiotherapy. Eight patients were treated by abdominoperineal resection of the rectum (21.1%); one patient had local excision and one patient had nodal dissection. A diversion colostomy was performed in six patients—it was performed as an emergency in three, semiurgently on one and electively in two.

Fifteen patients received radiotherapy alone (39.5%) but only three were treated by chemotherapy alone (7.9%). Combination chemotherapy and radiotherapy was given to 14 patients (36.8%). Thus, 76.3% of patients had some form of radiotherapy either alone or in combination and 44.7% had chemotherapy either alone or in combination. The treatment of choice in our institution seemed to be radiotherapy with or without chemotherapy.

Relatively more males than females had both anal canal and anal margin tumors (1:0.5 versus 1:0.7). Patients with anal margin tumors were on the average ten years older than patients with anal canal tumors. Overall there were twice as many patients with anal canal tumors as anal margin tumors. There was no difference in frequency of previous anal problems in the two groups. One third of anal canal and anal margin tumors were situated anteriorly. Histological types were roughly equal in each group. There were more node-positive patients with anal margin tumors (54.2% versus 41.6%). Anal canal tumors tended to be less well-differentiated (poorly differentiated—54.2% versus 33.3%). More patients with anal margin tumors were managed by abdominoperineal resection of the rectum (25% versus 16.6%). Radiotherapy was used more frequently in anal margin tumors (50% versus 37.5%) but combination therapy was more common in anal canal tumors (45.8% versus 16.6%).

Follow-up was inadequate in most patients. Sixteen patients (42.1%) were not followed after their first clinic visit because they failed to attend for further clinical appointments. Twenty-two patients were followed-up between one to more than eight years, but only three patients were followed and were alive after eight years.

TABLE 3. *Histopathology.*

Histology	Number
Squamous cell	27
Epidermoid	3
Basiloid	3
Cloacogenic	5

TABLE 4. *Patients treated surgically.*

Surgery	Number
None	23
Abdominoperineal resection	8
Local excision	1
Colostomy	6

TABLE 5. *Patients treated with radiotherapy and chemotheapy.*

Treatment	Number
Chemotherapy	3
Radiotherapy	15
Both	14
None	6

Discussion

This study is the first one in the Kingdom which addresses the problem of SCCA. While the numbers in the series are to some extent biased (see introduction) and the numbers are small, they form a basis for future studies.

In comparison with the West [7], patients treated in our institution had a different male:female ratio (1:0.58 versus 1:12) whereas the median age was similar [1]. The method of presentation was also comparable to that of the West [2,4], namely bleeding, a lump and pain. Most of the patients in the present study presented at a late stage of their disease (73.7%—T_3 or T_4) and only 26.3% presented at either stage T_1 or T_2. Most Western patients (especially those with tumors of the anal margin) tend to present early as either T_1 or T_2 [7].

The rate of inguinal lymph node involvement at presentation was 28.9% in our series compared to only 11% in another study [7]. Many studies report nodal involvement rates of 30% to 40%, however [2,7]. The presence of other metastatic disease at presentation surprisingly was similar to that described in the West (12.8% versus 10%) [1].

It has been suggested that chronic anal conditions can predispose to SCCA [2] and this was confirmed in our study which showed 36.8% of patients with a previous history of benign anorectal disease.

There were marked differences between the present study and Western data relating to the age, male to female ratios, surgery, site and predisposing factors of anal canal and anal margin tumors. In the St. Marks Hospital series [1], there was a predominance of females with anal canal tumors but this sex difference was not observed in this study. Whether this was due to a decreased incidence of females with tumors or a high incidence of the disease in males cannot be determined since true incidence rates cannot be calculated in the Kingdom. We have observed a similar sex incidence reversal (unpublished data) in relation to right-sided colonic tumors in the Kingdom but it is not explained. Anal canal tumors were predominantly poorly differentiated in comparison with tumors of the anal margin. This finding may be due to exceptionally high levels of anal hygiene in the Kingdom and therefore more well-differentiated anal margin tumors. It has been found that poor perianal hygiene is associated with a higher incidence of anal margin tumors [2]. There was no difference in the frequency of predisposing diseases between anal canal and anal margin tumors and this may be related to the clothing worn in the Kingdom. It has been suggested that tight irritant clothing may predispose to anal irritation and thus to anal margin tumors [1,2]. This would clearly not be true in the Kingdom where the thobe would be the clothing style of choice.

Unfortunately, survival information according to the different modalities of treatment cannot be obtained because of lack of follow-up. During the study period the preferred treatment for SCCA in our institution seems to have been radiotherapy although combination therapy was given to 37% of the patients. Twenty-three percent of patients were treated by abdominoperinal resection but most of these patients were treated in the first years of the study when radical surgery was considered to be the treatment of choice and radiotherapy was reserved for inoperable tumors.

The age and sex of our patients and the differentiation of their tumors may represent the disease characteristics of a "low incidence" country, but outside of a prospective data set, it would be difficult to further comment upon this problem. Anal cancers represent about 3% of all anorectal tumors in the West [1] but in our cancer registry they represented 13.3% of anorectal tumors which in themselves are probably about ten times less frequent than they are in the West (Kuwait National Cancer Register). The incidence of anal cancer in the Kingdom is low and the disease characteristics of a "low incidence" country may be different from those in the West. Why tumors should be less well-differentiated, why sex differences should be reversed or why patients should be older remain in question. Unfortunately, the present study does not shed light on these problems. It does, however, document the disease, it identifies differences and hopefully others in the future will be able to trace the differences further—the establishment of a national cancer registry would be one important step towards further data collection and future prospective analysis.

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EPIDEMIOLOGICAL SURVEY OF SPINAL CORD INJURY: A STUDY OF 377 PATIENTS

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بلغ عدد المرضى الذين أدخلوا وحدة اصابات النخاع الشوكي في مستشفى الرياض المركزي في الرياض بالمملكة العربية بالسعودية ٤٥٠ مريضا بين شهري يونيو ١٩٧٩م ومارس ١٩٨٤م. تمت دراسة حالات ٣٧٧ منهم (٣٦٩ ذكور و٨ اناث) من ذوي السجلات الكاملة والإصابات الرضحية. قسم المرضى إلى أربع مجموعات: عنقية، وظهرية، وظهرية قطنية، وقطنية. درست لدى كل مجموعة المعالم التالية: السن، والجنس، والجنسية، وطول المدة التي سبقت الدخول إلى المستشفى وجهة الإحالة. صُنفت أسباب الإصابة في أربع مجموعات تضمنت الحوادث المروية، والإصابات الصناعية، والإصابات المنزلية، وجروح العيارات النارية. تضمنت الدراسة نمط الإصابة العظمية والإصابات المرافقة، والمضاعفات وقت الدخول وخلال سير العلاج بالمستشفى والعجز العصبي وتقدم الحالة. تم عرض نتائج المعالجة في عدد من الجداول مع شرح لها في متن الدراسة. من المؤمل أن تكون هذه الدراسة بمثابة دليل على حجم مشكلة إصابات النخاع الشوكي في المملكة العربية السعودية وأن تلقى الضوء على الصعوبات التي واجهتنا ومن ثم وضعت اقتراحات مؤقتة لإصلاحها.

The total number of patients admitted to the Spinal Cord Injury Unit, Riyadh Central Hospital, Riyadh, Saudi Arabia from June 1979 to March 1984 approached 450 patients. Of those, 377 (369 males and 8 females) patients with complete records and sustaining traumatic injury were studied. The patients were divided into four groups: cervical, dorsal, dorsolumbar and lumbar. In each group, the following parameters were studied: age, sex, nationality, length of period prior to admission, and source of admission. The cause of injury was divided into four groups, including road traffic accident, industrial injuries, domiciliary injuries and gunshot wounds. The study included the type of bony injury and associated injuries, complications both on admission and during hospital course and neurological deficit and progress. The results of treatment are displayed in a variety of tables with explanations in the text. It is hoped that this work would be a pointer to the size of the problem in Saudi Arabia, and would highlight the difficulties encountered and tentatively put forth suggestions for correction.

"Spinal cord injury, which often results in permanent paralysis, is one of the most serious forms of trauma experienced by man." The incidence was reported in the United States as 12.4 to 53.4 cases per million population per year [1]. It is also reported as 13 to 27 per million per year and 50 to 68 cases per million per year including sudden death [2,3]. There is no available accurate epidemiological information on the incidence of spinal cord injury in Saudi Arabia, but it could be as high as that of the United States [4]. Spinal cord injury is most prevalent in young people with 80% of the patients younger than 40 years of age with predominancy of males [5], the most common cause being motor vehicular accidents [6].

Most frequently involved levels are the lower cervical and thoracolumbar junctions. As reported by the National Spinal Cord Injury Data Research Center in Phoenix, Arizona, USA, 53% of spinal cord injuries result in quadriplegia and 47% in paraplegia [7].

The question of treatment remains controversial—from no bony treatment to decompressive laminectomies to fusion and plating—with the use

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of various techniques [8]. In the management of thoracolumbar injuries, polarization around two extremities emerged: surgical versus nonsurgical treatment [4]. The purpose of this study is to describe the incidence and distribution, the bony lesions and their management and the results of treatment in the experience of the Spinal Cord Injury Unit, Riyadh Central Hospital, Riyadh, Saudi Arabia.

The Unit

The present study is a personal retrospective study carried out in the Spinal Cord Injury Unit, Riyadh Central Hospital, Riyadh, Saudi Arabia. The unit was a converted orthopedic ward with 36 beds, 26 ordinary beds and ten with Stryker frames. This unit accepts only male patients, the females are still admitted into the ordinary orthopedic ward. The unit is equipped with its own gymnasium annexed to the unit. There is gross deficiency in the medical and paramedical staff looking after the unit. The staff to patient ratio approaches one to six. While this is far below ideal [9], help is easily accessible from the surgical and medical specialties within the hospital.

Material and Methods

The total number of patients admitted to the Spinal Cord Injury Unit, Riyadh Central Hospital, Riyadh, approached 450 patients from June 1979 to March 1984. Of those, 377 (369 males and 8 females) of pure traumatic patients with complete records were studied. The patients were divided into four groups: (1) cervical (C1 to C7, inclusive), (2) dorsal (T1 to T10, inclusive), (3) dorsolumbar (T11, T12, L1, L2), (4) lumbar (L3, L4, L5).

In each group, the following parameters were studied: age, sex, nationality, length of period prior to admission, and source of admission as direct or referred from another hospital. The cause of injury was divided into four groups including traffic accidents, industrial injuries, domiciliary injuries and gunshot wounds. The study included the type of bony injury, associated injuries, complications both on admission and during hospital course, and neurological deficit and progress. Specially constructed forms with all the required data were used for each patient, and data was extracted and analyzed from them. The progress and evaluation of the neurological deficit was done according to the grid method of Frankel et al [8], where "A" denotes complete lesion, "B" denotes sensory sparing, "C" denotes useless motor function, "D" denotes useful motor function and "E" denotes normal neurological status.

The treatment utilized was both conservative and surgical. In the cervical group (158), 136 patients were treated conservatively with skull traction and only 22 underwent surgical treatment. Of the dorsal group (48), 43 patients were treated conservatively and five by surgical means. Of the dorsolumbar group (155), 71 patients were treated conservatively and 84 by surgical means. In the lumbar group [16], seven patients were treated conservatively and nine patients were treated by surgical means.

All received standard physiotherapy treatment from the time of admission and were rehabilitated to the maximum level that could be attained in the unit.

Results

The most frequent age group was 21 to 30 years (136), constituting 36.1%. Only eight patients were females (2.1%). Of those, three were cervical and five were dorsolumbar injuries. Of all the patients, 146 were Saudi and 211 were non-Saudi.

The source was direct referral to the hospital (163) and indirect from other hospitals (214). One hundred ninety-one (50.7%) patients were admitted within 24 hours, 49 (13%) within 48 hours, 60 (16%) within one week, and 77 (20.3%) over one week.

The cause of injury when analyzed showed car accidents constituting 63.9% (241) of the total, industrial injuries 26.5% (100), and domiciliary injuries 8.2% (31). Only five patients (1.3%) presented with gunshot injuries. The number broken down into different etiological factors in relation to the various subgroups is shown in Table 1.

The neurological classification, incidence and extent of the injuries on admission to the unit shows 171 patients (45.4%) were with complete neurological injuries. Of those, 74 (19.6%) were quadriplegic and 97 (25.7%) were paraplegic. One hundred fifty-eight patients (41.9%) were incomplete neurological injuries. Of those, 57

TABLE 1. *Cause of injury and total percentage of the various etiological factors in all groups.*

	Cervical (%)	Dorsal (%)	Dorsolumbar (%)	Lumbar (%)	Total
Road traffic accident	130 (82.3)	34 (70.8)	70 (45.2)	7 (43.8)	241 (63.9)
Driver	69	18	39	4	130
Passenger	42	10	22	0	74
Pedestrian	5	0	5	1	11
Not known	14	6	4	2	26
Industrial	19 (12.0)	9 (18.8)	65 (41.5)	7 (43.8)	100 (26.5)
Fall	11	7	44	4	66
Heavy object	8	2	21	3	34
Domiciliary	8 (5.1)	3 (6.3)	19 (12.3)	1 (6.3)	31 (8.2)
Fall	8	1	16	1	26
Heavy object	0	2	3	0	5
Gunshot	1 (0.6)	2 (4.2)	1 (0.6)	1 (6.3)	5 (1.3)
	1	2	1	1	5
Total	158	48	155	16	377

(15.1%) were incomplete quadriplegics, 101 (26.8%) were incomplete paraplegics, and 48 patients (12.7%) were neurologically free.

The pattern of associated injuries shows head injuries constituted 20.2% (76) of the total, chest injuries 18% (68), abdominal injuries 5% (19), pelvic injuries 4.8% (18), and fracture of the extremities 17% (64) of all the cases.

Of the total number of admissions, the highest rate of complications during hospitalization was urinary tract infections at 41.6% (157) compared to 85 (22.5%) on admission. Pulmonary complications constituted 1.6% during hospitalization compared to 5.6% on admission.

Analysis of treatment in the various groups showed: in the cervical group, out of 158 patients, 136 (86.1%) were treated conservatively and 22 (13.9%) were treated surgically, 16 (10.1%) by posterior fusion and wiring, and 6 (3.8%) by anterior decompression and bone grafting. Out of 73 patients with complete lesions, 23 (31.1%) became incomplete and none deteriorated with a total percentage (38.6%) of recovery of some function.

Of the 48 patients in the dorsal group, 43 (89.6%) were treated conservatively and only five (10.4%) were treated surgically; four (8.3%) by anterior decompression and one (2.1%) by Harrington Rod fixation and posterior fusion. Out of 39 patients with complete lesions, six (12.8%) became incomplete; none deteriorated with a total percentage (20.8%) of recovery of some function.

Of the 155 patients in the dorsolumbar group, 71 (45.8%) were treated conservatively and 84 (54.2%) were treated surgically; 50 (32.3%) by Harrington Rod fixation and posterior fusion, six (3.9%) by anterior decompression alone, and 28 (18.1%) by both anterior decompression and Harrington Rod fixation. Out of 56 patients with complete lesions, ten (17.9%) became incomplete with a total percentage (38.7%) of recovery of some function.

Of the 16 patients in the lumbar group, seven (43.8%) were treated conservatively and nine (56.2%) were treated surgically by Harrington Rod fixation and posterior fusion. Only one was complete and recovered to an incomplete level. The total percentage of recovery of some function in the group was 62.5%.

The type of mobilization achieved versus neurological status on discharge is shown in Table 2.

The mortality results are shown in Table 3. The total mortality in the hospital was 41 out of 377 (10.9%). The highest incidence is noticed in the cervical group constituting 21.5% of the total and 82.9% (34) in relation to total mortality. High mortality rates were noted in complete lesion, 82.9% (34) compared to incomplete lesion, 17.1% [7]. No mortality was recorded in the lumbar group.

TABLE 2. *Type of mobilization versus neurological deficit on discharge with percentages of the total in each group.*

Type of	Cervical						Dorsal						Dorsolumbar						Lumbar					
mobilization	No.(%)	A	B	C	D	E	No.(%)	A	B	C	D	E	No.(%)	A	B	C	D	E	No.(%)	A	B	C	D	E
Walking with no support	22(13.9)	–	–	–	7	15	2(4.2)	–	–	–	–	2	30(19.4)	–	–	–	11	19	4(25.0)	–	–	–	–	4
Walking with support	53(33.5)	–	1	4	21	27	14(29.2)	5	2	3	4	–	78(50.3)	17	2	10	39	10	10(62.5)	–	1	1	7	1
Wheelchair independent	7(4.4)	–	–	3	4	–	9(18.8)	8	1	–	–	–	8(5.2)	8	–	–	–	–	1(6.3)	–	–	–	1	–
Wheelchair assisted	32(20.3)	16	–	13	3	–	15(31.3)	15	–	–	–	–	20(12.9)	13	3	2	2	–	0	–	–	–	–	–
Bed level	44(27.8)	34	4	4	2	–	8(16.7)	7	–	1	–	–	19(12.3)	10	1	5	2	1	1(6.3)	–	–	–	1	–
Total	158	50	5	24	37	42	48	35	3	4	4	2	155	48	6	17	54	30	16	–	1	1	9	5

Mortality versus age group is shown in Table 4. In the 20 year or younger age group, the mortality rate constituted 4.6% (two of 44); in the 50 year or older age group, the rate increased to 21.6% (eight out of 137 patients).

Mortality versus associated injuries showed 19 out of 41 deaths had associated injuries (46.3%), the most common being head injuries which constituted 22% (9/41).

The most common cause of death was acute cardiopulmonary failure encountered in 20 out of 41 deaths, constituting 48.8%. Only one patient (2.4%) died of uremia.

TABLE 3. *Mortality incidence and causes.*

Group	Total no.	Died no.	Complete	Incomplete
Cervical	158	34	30	4
Dorsal	48	2	1	1
Dorsolumbar	155	5	3	2
Lumbar	16	0	0	0
Total	377	41	34	7

TABLE 4. *Distribution by age and mortality in each age group.*

	Age group (years)				
Group	11 to 20	21 to 30	31 to 40	41 to 50	>50
Cervical	23	45	36	31	23
Dorsal	5	19	17	3	4
Dorsolumbar	14	64	39	29	9
Lumbar	2	8	3	2	1
Total	44	136	95	65	37
Mortality (%)	2(4.5)	12(8.8)	10(10.5)	9(13.8)	8(21.6)

Discussion

The age distribution in our patients showed a high prevalence within age groups 21 to 30 years (36.1%). Those who were younger than 40 years of age constituted 72.9%. This compared with other reports [1,5,10,11].

Motor vehicular accidents constituted the most common cause for traumatic spinal cord injuries [5,11–13], particularly in Saudi Arabia [14]. This was the cause in 63.9% of our patients.

The sex distribution showed a predominance of males with very few females (2.1%). In other reports, the female distribution was 10% to 30% [1,8,11]. The lower incidence of females in our report was probably related to the social habits in Saudi Arabia where females are more protected.

The higher percentage of late admissions to the unit was due to late referral from other hospitals in the area [5,11]. It is our impression that this affects both the prognosis and the mode of treatment in these patients. This study was not correlated due to incomplete records.

In associated injuries, head injuries showed the highest association with cervical and dorsal injuries (26% and 29%, respectively). Chest injuries showed the highest association with dorsal injuries (31.3%) while abdominal, pelvic and limb injuries were maximally associated with lumbar injuries (1.3%, 25% and 31.3%, respectively).

In this series, the most common injury was cervical and dorsolumbar region which is comparable to other reports.

Review of the mode of treatment showed a tendency toward conservative treatment in both cervical and dorsal groups, while more patients underwent surgical treatment in the dorsolumbar and lumbar groups. None of the patients showed deterioration.

The total percentage of recovery, regardless of the mode of treatment, was comparable in both cervical and dorsolumbar groups (38.6% and 38.7%, respectively). This was lower in the dorsal group (20.8%) and much higher in the lumbar group (62.5%) [8,15,16].

The rate of urinary tract infection was high both on admission and during hospitalization [12,13]. This reflects late referral to the hospital and inadequacy of treatment during hospitalization. More aggressive and strict measures need to be taken for the reduction of this serious complication.

During hospitalization bedsores occurred in 14.9% of the patients. This high percentage rate reflects the understaffing of the unit [9,13].

Pulmonary complications were low during hospitalization constituting 1.6% as compared to 5.6% on admission.

The degree of mobility attained was better in the paraplegic group than the quadriplegic group. None of the complete quadriplegics attained the level of walking with or without orthoses, while 58% (33/57) of the incomplete could. In the paraplegic group, 23.2% (22/95) of the complete and 79.2% (80/101) of the incomplete could attain the level of walking with or without orthoses.

The total mortality of 10.9% correlates with other reports [10,14], the highest being in the cervical group and in complete lesion more than incomplete. Mortality also increased with age (Table 1) and the presence of associated injuries, the most common being head injuries (22%).

Conclusion

As reported, spinal cord injury is common in Saudi Arabia. This paper reflects the clinical load of spinal injuries treated in Riyadh Central Hospital. Attention should be paid to the increase in motor vehicular accidents and measures of prevention to be taken. Careful documentation of case histories and establishment of a National Registry for Spinal Cord Injury is recommended. The quality of life of these patients could be improved by more aggressive and strict measures for prevention and treatment of bedsores and urinary tract infection. Improvement in the staffing percentage of the unit is needed.

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PERNICIOUS ANEMIA IN SAUDI ARABS

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شخصت على مدار خمس سنوات امتدت من شهر يناير ١٩٨٦م إلى شهر ديسمبر ١٩٩٠م سبع حالات من فقر الدم الوبيل لدى مرضى سعوديين، خمسة رجال وامرأتين، في مستشفى الملك خالد الجامعي في الرياض. تراوح سن المرضى بين ٤٥ و ٧٣ وكان متوسط العمر ٦١ عاما. كانت الأعراض والسمات المخبرية ونمط المرض مماثلة لما سبق وصفه لدى المرضى من شمال أوروبا، ربما باستثناء غلبة الذكور بين مرضانا. أبدى أحد المرضى ظاهرة مثيرة للاهتمام تمثلت بأن حجب وجود التلاسيمية الصغرى (بيتا) ظهور الكريات الكبرية المميزة لفقر الدم الوبيل. لم يظهر أي ترابط بين فقر الدم الوبيل لدى مرضانا وبين أي مرض آخر من أمراض المناعة للذات.

Over a five-year period extending from January 1986 to December 1990, seven cases of pernicious anemia in Saudi patients were diagnosed at King Khalid University Hospital in Riyadh. There were five males and two females. The age range was 45 to 73 with a mean age of 61 years. The presenting symptoms, laboraotry features and the disease pattern were similar to those described in northern European patients with the possible exception of male predominance in our patients. One patient demonstrated an interesting phenomenon of masking the macrocytosis of pernicious anemia by concurrent beta thalassemia minor. No association with any other autoimmune diseases was detected in any of our patients.

Pernicious anemia (PA) predominates in people of northern European origin, but may affect others more often than previously thought. Arabs are among the ethnic groups described to be rarely affected by PA [1]. Only a few case reports of Arabs with PA have appeared in the literature. Two case reports of Saudi patients with PA have appeared in the Saudi literature [2,3]. In this report, we describe details of clinical, laboratory and immunologic features in seven adult Saudi patients seen at our institution. To the best of our knowledge, this is the first report to describe a series of Saudi patients with PA.

Patients and Methods

Between January 1986 and December 1990, a total of 13 cases of megaloblastic anemia occurring in adult Saudi patients were diagnosed at King Khalid University Hospital (KKUH) in Riyadh. Four of 13 cases had no etiological diagnosis because of incomplete work-up. Two other cases were associated with pregnancy and found to be secondary to folate deficiency. The remaining seven patients had pernicious anemia.

The Saudi Arab origin of those patients was ascertained by the tribal descent in four patients, the family surname in two and by direct questioning in the remaining patient.

The criteria used to diagnose PA were similar to those proposed by Lidenbaum in 1983 [4]; namely, (a) the presence of megaloblastic bone marrow, (b) subnormal serum vitamin B_{12} level, (c) characteristic vitamin B_{12} absorption (Schilling) test or the presence in the serum of anti-intrinsic factor antibodies (AIFA).

None of the patients had a history of gastrectomy or ileal resection. In addition to detailed his-

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tory and complete physical examination at presentation, all seven patients underwent full hematological evaluation including bone marrow examination, biochemical testing for blood glucose, renal function, liver enzymes, serum bilirubin, lactate dehydrogenase levels, and thyroid indices. All patients had ABO and Rh blood grouping determined according to the standard technique. Serum B_{12} and folate levels were measured by radioimmunoassay (vitamin B_{12}/folate dual RIA kit, Amersham, UK).

All seven patients were tested for the presence of AIFA using radioisotope assay as described by Goltlieb et al [5]. Anti-parietal cell antibodies (APCA) were tested for in five patients using indirect immunofluorescence technique [6]. Gastroscopy with fasting gastric Ph determination (without stimulation) and multiple gastric biopsies were obtained in all patients.

Dual isotope Schilling test (Dicopac Kit, Amersham, UK) was carried out in five patients. Two capsules, one containing ^{57}CO cyanocobalamin bound to intrinsic factor and the other containing free ^{58}CO cyanocobalamin were given orally to each of the five patients. This was immediately followed by 1000 μg of non-radioactive vitamin B_{12} given intramuscularly as a flushing dose. A differential count of the isotope was then carried out on 24-hour urine. The ^{57}CO/ ^{58}CO urinary B_{12} ratio above 1.8 was considered a positive test indicating intrinsic factor deficiency.

All patients received intramuscular vitamin B_{12} therapy. Four patients were treated initially with 1000 μg cyancobalamin daily for three days followed by monthly injections of the same dose, while the remaining three patients were given 1000 μg of vitamin B_{12} daily for three consecutive days followed by weekly injections of the same dose for four weeks and maintained thereafter on monthly injection of the same dose of Vitamin B_{12}. All patients were also given 5 mg of folic acid daily in conjunction with parentral vitamin B_{12} therapy from the time the diagnosis of megaloblastic anemia was made until the diagnosis of B_{12} deficiency was established.

Results

Age and Sex

There were five males and two females with ages ranging from 45 to 73 years with a mean age of 61 ± 11 (mean ± SD) years.

Symptoms and Signs at Presentation

The most frequent symptom at presentation was fatigue which was reported by more than half of the patients. The most frequent sign at presentation was, as expected, pallor. Other symptoms and signs are shown in Tables 1 and 2, respectively.

Diagnostic Studies

The results of the laboratory parameters for individual patients and confirmatory tests are shown in Tables 3 and 4, respectively. All seven

TABLE 1. *Symptoms at presentation.*

Symptoms	Number of patients (N = 7)	Percentage
Fatigue	5	71
Symptoms of anemia	4	57
Weight loss	2	28
Anorexia	2	28
Painful tongue	1	14
Fever	1	14
Neurological symptoms	1	14
Skin lesions	0	0
Symptoms of thyroid diseases	0	0
Premature graying of hair	0	0
Symptoms related to diabetes	0	0

TABLE 2. *Signs at presentation.*

Sign	Number of patients (N = 7)	Percentage
Pallor	7	100
Glossitis or smooth tongue	2	28
Jaundice in the presence of normal liver enzymes	1	14
Peripheral neuropathy	1	14
Posterior column signs	0	0
Goiter	0	0
Signs of hypothyroidism or hyperthyroidism	0	0
Skin hypopigmentation or hyperpigmentation	0	0
Splenomegaly	0	0

patients had normal thyroid functions, serum folate levels, blood glucose and renal function.

Response to Therapy

Reticulocytosis was first seen after two days of treatment in two and following three days in five patients. The maximum reticulocyte count was obtained between the fifth and the eighth days following initiation of treatment in all patients. All patients, except No. 7 normalized their hematological and other laboratory parameters within six to ten weeks. Patient No. 7 maintained a hemoglobin level of 130 g/l four months after starting therapy. The two thrombocytopenic patients normalized their platelet count within the first two weeks of therapy.

Discussion

Although PA was traditionally considered to be a disease of people of northern European origin, recent surveys in racial groups in whom the disease was widely regarded as rare such as American Blacks, American Indians, Latin-Americans and Asians suggests a higher incidence in them than previously thought [7-11]. Arabs are considered to be one of the racial groups that are rarely affected by PA [1]. The first report of possible PA

TABLE 3. *Laboratory parameters for individual patients.*

Patient's number	Age	Sex	WBC $\times 10^9$/L	HB g/L	HCT %	MCV (fl)	Platelets $\times 10^9$/L	Retics %	(a) LDH	(b) T. Bil	(c) B12	Blood Group	Remarks
1	67	F	5.2	58	17.5	120.0	60	2	2832	26	22	A+	
2	65	M	6.8	90	24.9	112	299	2	440	54	24	A+	With normal liver enzymes and serum alkaline phosphatase
3	71	F	7.4	69	21.0	126	322	1	427	13	21	O+	
4	48	M	5.7	65	19.2	114	213	0.5	1814	36	24	A+	
5	45	M	6.9	110	34.4	121	364	1	824	26	40	A−	
6	61	M	4.6	66	19.8	123	76	1	3158	34	56	B+	
7 (d)	73	M	4.8	71	22.2	90.5	177	0.5	1040	17	26	0+	HbA2 = 6%

(a) Lactate dehydrogenase, normal range 140–300 μ/L; (b) total bilirubin, normal range 1–17 μg/L; (c) normal range for B12: 165–920 μg/L, values less than 100 μg/L considered deficiency state; (d) this patient has combined B12 deficiency and *beta*-thalassemia trait (see Discussion).

TABLE 4. *Results of diagnostic and confirmatory tests.*

Patient number	Bone marrow	Fasting gastric Ph	Gastroscopy/ gastric pathology	(a) Schilling test	(b) APCA in serum	(c) AIFA in serum
1	Megaloblastic	6.99	Gastric atrophy with intestinal metaplasia	Positive	Present	Present
2	Megaloblastic	7.00	Chronic gastritis with intestinal metaplasia	Positive	NA (d)	Absent
3	Megaloblastic	7.2	Atrophic gastritis	NA	Present	Present
4	Megaloblastic	7.6	Chronic gastritis	Positive	Absent	Present
5	Megaloblastic	6.84	Normal gastric mucosa	Positive	Absent	Absent
6	Megaloblastic	7.2	Chronic gastritis	NA	Present	Present
7	Megaloblastic	8.0	Normal gastric mucosa	Positive	NA	Present

(a) A positive Schilling Test refers to the pattern compatible with the absence of gastric intrinsic factor; (b) anti-parietal cell antibody in the serum; (c) anti-intrinsic factor antibody in the serum; (d) NA refers to tests either not done or result is not available.

in two Arab patients came out of Iraq in 1952 [12]. Three additional cases of PA were reported from Kuwait in 1970 [12]. Recently, there have been two case reports of PA occurring in Saudi Arabs [2,3]. To the best of our knowledge, our series, although small, is the first to describe a group of Saudis and probably of Arab patients with PA.

The disease in our patients shows many similarities to that described in medical textbooks occurring predominantly in northern Europeans. These similarities include the mean age incidence, the clinical presentation, response to therapy and the frequency of both APCA and AIFA which were detected in the sera of three out of five (60%) and five out of seven (70%) patients respectively [1]. In addition, blood group A was the predominant blood group among our patients and occurred in four out of the seven patients (57%). Although the exact frequency of different ABO blood groups among Saudis is not well defined, the limited number of small studies conducted for this purpose suggests a frequency of blood group A of about 30% in the indiginous Saudi Arab [13,14].

The clinical manifestations of the disease were not different from those reported in Caucasians. The incidence of thyroid disorders, skin pigmentary changes, diabetes mellitus and gastric malignancies does not seem to be increased. It, however should be mentioned that a solid conclusion regarding the latter statement cannot be drawn due to the small number of patients studied.

A notable observation in this series is the male predominance which contrasts the higher female or at least the about equal sex-incidence reported in Caucasians [1,15]. This observation, however, may not be statistically significant but is of interest and may reflect an aberration in the disease behavior when it affects Arabs. This latter assumption is further suggested by the male predominance in the previously reported five cases of PA occurring in Arabs since two out of three patients reported from Kuwait and both Saudi patients reported were male [2,3,12].

It is generally accepted that the frequency of leukopenia, neutropenia and thrombocytopenia is related to the severity of anemia, being higher when the hematocrit falls below 25% [1]. None of our patients had significant leukopenia or neutropenia and only two patients had significant thrombocytopenia although six had a hematocrit of less than 25% at diagnosis. Thus, the best description for such an observation is that this relationship is not well-demonstrated in our small series.

Patient No. 7 demonstrates the interesting phenomenon of masking the macrocytosis of PA by concurrent *beta*-thalassemia trait. This phenomenon has been reported to occur with both *alpha*-[16] and *beta*-thalassemia [17] as well as with iron-deficiency anemia [18,19]. The mean corpuscular volume of this patient dropped to 70 fl four weeks following initiation of parenteral vitamin B_{12} treatment while the hemoglobin increased to 125 g/l.

Our series emphasizes the same point the authors of the two previous case reports presented, that is, PA, although rare, remains the diagnosis to consider in Saudi patients when they present with macrocytic anemia. In addition, due to the relatively high carrier rate of the thalassemic gene in the region [20], physicians should always consider the diagnosis of PA even in the absence of frank macrocytosis if the clinical setting suggests an acquired unexplained anemia in a middle age or elderly Saudi patient.

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DETECTION OF PNEUMOCOCCI WITH INCREASED RESISTANCE TO PENICILLIN AND THEIR CLINICAL SIGNIFICANCE

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تم فحص عقديات ذات الرئة المعزولة من الدم ومن السائل الشوكي ومن الجهاز التنفسي وعينات سريرية أخرى مأخوذة من ٦٢٦ مريضًا وذلك لتقصي حساسيتها للبنسيلين. تم جمع البكتيريا من مرضى في مستشفيات مختلفة في الرياض، بالمملكة العربية السعودية. وباستخدام قرص يحوي مكروغرام واحد من الأوكسباسلين تبين أن ١٤٧ (٢٣٫٥٪) من العينات المعزولة مقاومة للبنسيلي نسبيا. بينما تبين بفحص المقاومة النسبية للبنسلين على ٣٥٨ من العينات المعزولة باستخدام أقراص تحوي وحدة أو عشر وحدات من البنيسيلين ومقارنتها مع التركيز الأدنى لمنع نمو الجراثيم أو مع قرص أوكساسيلين، بلغت نسبة الخطأ في التقدير الإيجابي في الحساسية للبنسيلين ١٨٪. ولما كانت المكورات الرئوية سببا لالتهابات جرثومية خطرة على الحياة، مثل التهاب السحايا، وإنتان الدم وذات الرئة، فإن تحديد حساسيتها للبنيسيلين بطريقة صحيحة لأمر شديد الأهمية.

Streptococcus pneumoniae isolates from blood, CSF, respiratory tract and other clinical specimens from 626 patients were tested for sensitivity to penicillin. The bacteria were collected from patients in different hospitals in Riyadh, Saudi Arabia. Using 1 μg oxacillin disk, 147 (23.5%) of these isolates were found to be relatively resistant to penicillin (RPR). When 358 pneumococcal isolates were tested for RPR using 1 or 10 unit penicillin disks and compared with the MIC or oxacillin disk, as many as 18% were incorrectly designated as sensitive by penicillin disks. Since pneumococci can cause potentially life threatening infections like meningitis, septicemia and pneumonia, the significance of determining their correct susceptibility to penicillin cannot be over emphasized.

Streptococcus pneumoniae is a leading cause of meningitis, bacteremia and other serious diseases. Despite availability of new antimicrobial agents, *S. pneumoniae* remains an important cause of human disease and death. Increased resistance of pneumococci to penicillin G was reported by Eriksen in 1945 [1]. It was later recognized in the United States, Australia, New Guinea, England, Saudi Arabia, and in many other countries [2–8]. The majority of the isolates have been found to be relatively penicillin-resistant (PRP) with minimal inhibitory concentration (MIC) of 0.1–1.0 μg/ml, their prevalence varying from a low of 1.3% to a high of 51% in different parts of the world [5,6,9,10]. Thus, it is important to recognize the incidence of resistance in a particular geographical location for both epidemiological and therapeutic reasons. Of the four previous studies on the occurrence of RPR in Saudi Arabia, only one reported an incidence of 31%, and three found all pneumococcal isolates to be susceptible to penicillin [5,8,11,12]. It was suggested that this may have resulted from the differences in methodology [5]. In this paper, we report the prevalence of RPR in Riyadh and optimal methods for their detection.

Material and Methods

A total of 626 strains of *S. pneumoniae* isolated from clinical specimens from patients in Riyadh were used during this study. The isolates were identified by conventional methods (alpha hemolysis, optochin sensitivity and bile solubility)

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as described by Facklam and Carey [13]. The bacteria were isolated from blood, cerebrospinal fluid (CSF), respiratory tract and various other sources from different hospitals in Riyadh, with 43% of the isolates coming from King Faisal Specialist Hospital and Research Centre. Disk diffusion tests were performed on all isolates using commercially prepared 1 μg oxacillin disks (BBL, Cockeysville, Maryland, USA). A total of 358 *S. pneumoniae* isolates were also tested for RPR using both 1 μg oxacillin disks, one and ten unit penicillin disks and determination of MIC by tube dilution method. Antibiotics susceptibility testing was performed according to the methodology recommended by the National Committee for Clinical Laboratory Standards [14,15]. Mueller Hinton sheep blood (5% v/v) agar plates, pH 7.2 to 7.4, were used for disk diffusion as well as agar dilution tests. All incubations were at 35°C for 18 to 24 hours. Microorganisms were considered susceptible to oxacillin if the zone size was equal to or greater than 20 mm, RPR if the zone size was 13 to 19 mm and resistant if the zone size was less than 12 mm. Zone sizes of > 20 mm and < 19 mm for penicillin were considered susceptible and resistant, respectively.

Results

Of the 626 strains of pneumococci tested, over 70% were isolated from extrapulmonary sites (Table 1). When tested with 1 μg oxacillin disk or determination of MIC to penicillin, 23.5% were found to be RPR. Since some laboratories use penicillin disks for the detection of RPR, we tested 358 of these isolates by simultaneously using one and ten unit penicillin disks, 1 μg oxacillin disks and by MIC determination. Eighty-one percent of these isolates had an MIC of < 0.1 μg/ml and all were found to be susceptible by 1 μg oxacillin disks (Table 2). However, four and two of these isolates were recorded as resistant when disks containing one unit and ten units of penicillin, respectively, were used.

Of the 64 RPR isolates, all were correctly identified by oxacillin disk, but 16 to 22% were misidentified as susceptible by penicillin disks. All the four strains with an MIC of > 1.0 μg/ml for penicillin were correctly recorded as resistant when tested with either penicillin or oxacillin disks.

TABLE 1. *Source of pneumococcal isolates.*

Specimens	Number tested
Blood	65
Cerebrospinal fluid	9
Nose/pharynx	154
Sputum	171
Eyes/ears	178
Body fluid	12
Others	37
Total	626

TABLE 2. *Correlation between oxacillin and penicillin disks in 358 clinical isolates of pneumococci.*

Penicillin MIC μg/ml	Strains tested (n)	% Susceptible using 1 unit	10 units	Oxacillin disk 1 μg/ml
<0.1	290	98.6	99.3	100
0.1–1.0	64	21.8	15.6	0
>1.0	4	0	0	0

Discussion

It is no longer justifiable to assume that all isolates of *S. pneumoniae* are sensitive to penicillin. The incidence of increased resistance has remained variable in different geographical locations. The overall prevalence of 23.5% RPR we found in Riyadh is higher when compared with 1.3% in Canada, 4% in England, 12 to 15% in the USA, and 20% in South Africa, but lower when compared with 51% found in Spain [5,7,9,10,16,17]. Because of the variations in different geographical areas, it is desirable to recognize patterns of increased resistance for therapeutic and epidemiological purposes. Three previous studies using 50 isolates in Jeddah and 150 and 358 strains of *S. pneumoniae* in Riyadh did not detect any RPR or resistant pneumococci [8,11,12]. However, 31% of the 268 isolates from a tertiary care hospital in Riyadh were found to be RPR and the authors opined that this discrepancy might have resulted from differences in patient population and method of detecting RPR [5]. Close scrutiny of the four reports showed that 1 μg oxacillin disk was used by the latter investigators in Riyadh [5], two unit penicillin disks and MIC (with no details) in two earlier studies from a teaching hospital in Riyadh [8,11] and one from Jeddah [12] did not mention the method of testing. These discrepancies led us to retest the same 358 strains of pneumococci tested by Hussein [8] using oxacillin and penicillin disks and standardized agar dilution method [6,13,14,18]. Although none of these strains were recorded earlier as RPR by two unit penicillin disks, we found that 64 (18%) were RPR and 4 (1%) as resistant to penicillin. The inadequacy of penicillin disks to detect resistance among pneumococci has been documented previously [19,20]. Indeed, testing with penicillin disks may be hazardous because resistant isolates may appear to be sensitive. We concur with earlier workers and emphasize their recommendations [6,14,19–22] to use disks containing 1 μg oxacillin to detect increased resistance to penicillin. The only alternate method should be MIC determination using standardized techniques.

Although significant infections with pneumococcal strains fully resistant to penicillin are comparatively rare throughout the world, serious diseases caused by RPR are associated with high mortality and morbidity [23–25]. The clinical significance of RPR cannot be overemphasized especially in cases involving pneumococcal meningitis, septicemia or other serious infections. Hieber and Nelson [26] have shown that penicillin levels in CSF were considerably lower than simultaneous serum levels, particularly in the absence of meningeal inflammations. Peak penicillin concentration < 1.0 μg/ml are most commonly observed when standard penicillin doses are administered. Therefore, pneumococcal meningitis caused by RPR to penicillin may not respond to penicillin therapy. Indeed, all reports of relapses or prolonged illness have been in patients with meningitis [23–25].

Systemic infections due to *S. pneumoniae* are usually treated empirically with penicillin, pending susceptibility tests. In view of the occurrences of cases involving meningitis caused by RPR, the addition or substitution of vancomycin to this regimen is at present recommended [27–28]. In a recent review of the role of cephalosporins in the treatment of meningitis, Nelson [29] pointed out that RPR are killed by achievable concentrations of cefotaxime, ceftriaxare and vancomycin. Furthermore, vancomycin and imipenem were shown to be effective against a highly resistant pneumococcus in experimental meningitis in rabbits [30]. However, there is no clinical data by which to judge the efficacy of these drugs for RPR. Choice of initial therapy for pneumococcal disease in different communities must be based on such considerations as the age of the patient, underlying disease and knowledge of bacterial susceptibility to antimicrobial drugs of potential therapeutic value. We concur with Hussein [8] that clinical laboratories should test pneumococci for their susceptibility to penicillin but disagree with his recommendation that "the medical practitioners should not be deterred from using penicillin in the treatment of pneumococcal infection in this country because of emerging resistance elsewhere." Both RPR and penicillin resistant pneumococci appear to be here. Only the use of optimal methods will assure their detection.

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THE ASSOCIATION BETWEEN HEPATITIS C VIRUS ANTIBODY AND HEPATOCELLULAR CARCINOMA IN RELATION TO HEPATITIS B VIRAL INFECTION (RAFH EXPERIENCE)

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شوهد اثنان وأربعون مريضا مصابون بسرطان كبدي خلوي في مستشفى القوات المسلحة في الرياض بالمملكة العربية السعودية خلال عامين . وبما أن التهاب الكبد الفيروسي منتشر في المملكة فقد تمت أيضًا لدى هؤلاء المرضى دراسة الوَسَمة المصلية لالتهاب الكبد الفيروسي ب والتهاب الكبد الفيروسي ج الذي تم التعرف عليه مؤخرًا. ظهرت ايجابية المستضد السطحي لالتهاب الكبد بالحمة ب لدى أربعة عشر (٣٣ر٣٪) مريضا وإيجابية أضداد التهاب الكبد بالحمة ج لدى أحد عشر (٢٦ر٢٪) وإيجابية لكل من المستضد ب والضد ج لدى إثنين (٤ر٨٪) وظهرت إيجابية المستضد السطحي ب وأضداد التهاب الكبد بالحمة ج لدى خمسة (١١ر٩٪). وكانت نتائج الوَسَمة المصلية لدى ١٤٧٢ متبرعا بالدم (مجموعة ضابطة). اثنان وعشرون (١ر٥٪) منهم كانوا إيجابيين لضد التهاب الكبد بالحمة ج وتسعة وخمسون (٤٪) كانوا إيجابيين للمستضد السطحي لالتهاب الكبد بالحمة ب واثنان (٠ر١٪) كانا إيجابيين لكلا الواسمين. وتتوافق نتائج هذه الدراسة مع نتائج دراسات سابقة أجريت في أمكنة أخرى. ومن المفترض بأن التهاب الكبد بالحمة ج شأنه شأن التهاب الكبد ب قد يمثل سببا هاما من أسباب الإصابة بالسرطان الكبدي الخلوي في المملكة العربية السعودية .

Forty-two patients with hepatocellular carcinoma (HCC) were seen during two years at Riyadh Armed Forces Hospital (RAFH), Saudi Arabia. As viral hepatitis is common in this country, serological markers for hepatitis B virus (HBV) and the newly identified hepatitis C virus (HCV) were also studied in these patients. Fourteen (33.3%) patients were HBsAg positive, 11 (26.2%) were anti-HCV positive, two (4.8%) were positive for both HBsAg and anti-HCV and five (11.9%) were anti-HBc and anti-HBs positive. The remaining ten patients all were negative for markers. Serological markers were also studied in 1472 blood donors (control group) during the same period. Twenty-two (1.5%) were positive for anti-HCV, 59 (4%) for HBsAg and two (0.1%) for both markers. Our results are in accordance with previous studies carried out elsewhere, and it is suggested that hepatitis C virus like hepatitis B, may play an important etiological role in hepatocellular carcinoma in Saudi Arabia.

Hepatocellular carcinoma (HCC) is prevalent worldwide, particularly in developing countries where hepatitis B virus HBV infection is more prevalent [1–3]. Among HBV serum markers, HBsAg is a well recognized factor in hepatocarcinogenesis [4].

Following the recent development by Kuo et al [5] of a test for detecting anti-HCV as a marker of HCV infection, there have been several reports on a possible association of this viral infection with HCC [2,3,6–8]. However, the actual mechanism for oncogenic effect of anti-HCV has not been established.

In view of the high incidence of HCC [9], the endemicity of HBV [10] and the recent report on HCV infection in Saudi Arabia [11], we carried

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out a retrospective study to evaluate the prevalence of HBV markers and anti-HCV in Saudi patients with HCC.

Patients and Methods

Forty-two patients with histologically proven HCC were diagnosed between November 1988 and October 1990 at the Riyadh Armed Forces Hospital, Riyadh. Thirty-seven patients had fine needle aspiration [12] and five had needle liver biopsy. Upper abdominal ultrasound examination was done in all patients whereas abdominal computed tomographic (CT) examination was necessary in about only one-third of these patients. There were 38 males and four females (M:F = 9.5:1), 35 to 88 years of age (mean, 59.6 years). For this study 1,472 healthy blood donors were used as a control for measuring anti-HCV and HBaAg prevalence among Saudis. Tests for HCV antibody and HBV markers (HBsAg, anti-HBs and anti-HBc) were performed using the enzyme immunoassay kits supplied by Abbott, North Chicago, Illinois, USA. Alphafetoprotein (AFP) levels were measured using radioimmunoassay technique.

Results

Eleven (26.2%) HCC patients were anti-HCV positive, 14 (33.3%) were HBsAg positive, and two (4.8%) had both markers. Five (11.9%) patients had both anti-HBc and anti-HBs. In the remaining ten patients (23.8%) hepatitis B and C virus markers were not detected (Table 1). In the control group, 22 (1.5%) out of 1,472 blood donors were positive for anti-HCV while 59 (4%) were HBsAg carriers. Only two donors (0.1%) had both anti-HCV and HBsAg.

Alphafetoprotein values are shown in Table 2. Markedly elevated levels (> 1000 IU/L) were found in 35.7% of patients with HBsAg and 18.2% in anti-HCV positive group.

Discussion

It was noteworthy that about 25% of the HCC patients were anti-HCV positive. This finding is an extension of the various studies carried out elsewhere to evaluate anti-HCV in HCC [2,3,6–8] (Tables 3 and 4).

The prevalence of HBV antibodies (anti-HBc and anti-HBs) in our patients with HCC was only 12% while nearly one-quarter (23.8%) of the patients had no detectable viral hepatitis markers. A correlation seems unlikely between these antibodies and HCC in our HBV endemic area.

The frequency of both anti-HCV and HBsAg occurring together in an individual patient with HCC was relatively low (4.8%). However, in view of the small number of patients, this figure should be interpreted with caution. Whether the pres-

TABLE 1. *Viral hepatitis markers among 42 patients with HCC.*

	Anti-HCV	HBsAg	Anti-HCV and HBsAg	Anti-HBc and Anti-HBs	No markers	Total
Male	9 (21.4%)	13 (30.9%)	2 (4.8%)	4 (9.5%)	10 (23.8%)	38 (90.4%)
Female	2 (4.8%)	1 (2.4%)	0	1 (2.4%)	0	4 (9.6%)
Total	11 (26.2%)	14 (33.3%)	2 (4.8%)	5 (11.9%)	10 (23.8%)	42

TABLE 2. *Alphafetoprotein (AFP) levels in HCC patients with different markers.*

AFP IU/L	Anti-HCV	HBsAg	Anti-HCV and HBsAg	Anti-HBc and Anti-HBs	No markers
< 10	0	0	0	1 (20%)	3 (30%)
10–100	3 (27.3%)	3 (21.43%)	1 (50%)	1 (20%)	1 (10%)
100–500	1 (9%)	3 (21.4%)	0	1 (2%)	3 (30%)
500–1000	5 (45.5%)	3 (21.4%)	1 (50%)	2 (40%)	3 (30%)
> 1000	2 (18.2%)	5 (35.7%)	0	0	0
Total	11	14	2	5	10

ence of two markers may increase the risk of HCC [5] or not remains to be established.

There is a comparatively higher prevalence for anti-HCV alone and for anti-HCV with HBsAg in areas of high endemicity for HBV as reported from Taiwan [2], Mozambique [8] and South Africa [3]. In Saudi Arabia, which is an area of intermediate HBV endemicity [10], we observed lower prevalence of these two markers (Tables 1, 3, and 4). In low endemic areas of HBV infection (e.g. USA and Western Europe), higher prevalences of up to 75% for anti-HCV in HCC have been demonstrated [6,7,13] (Tables 3 and 4).

Alphafetoprotein (AFP) is a useful marker since it correlates with the disease progression, mass expansion and survival (14,15). Our data indicates lower AFP levels in HCC patients with anti-HCV compared to patients with HBsAg positivity.

In conclusion, HCV infection may have an etiological role in patients with HCC. This probably holds true for both areas of low and of high endemicity of HBV infection. Further long-term prospective studies are needed to confirm these observations.

TABLE 3. *Prevalence of HBsAg and Anti-HCV in patients with HCC from different localities.*

Origin	Total number studied	HBsAg	Anti-HCV
Saudi Arabia (RAFH)	42	14 (33.3%)	11 (26.2%)
Taiwan	66	42 (63%)	22 (33.3%)
South Africa	380	184 (48.4%)	110 (8.9%)
Spain	96	9 (9.3%)	72 (75%)
USA	87	28 (32%)	35 (40.2%)
Italy	132	41 (31%)	86 (65%)

TABLE 4. *Anti-HCV in HBsAg positive and negative patients with HCC.*

Origin	No. of HBsAg positive patients	Anti-HCV	No. of HBsAg negative patients	Anti-HCV	Total number of patients
Taiwan	42	7 (16.6%)	24	15 (62.5%)	66
South Africa	184	47 (25.5%)	196	63 (32%)	380
Spain	9	5 (56%)	87	67 (77%)	96
USA	28	4 (14.2%)	59	31 (52.5%)	87
Italy	41	22 (53.7%)	91	64 (70.3%)	132
Saudi Arabia (RAFH)	16	2 (12.5%)	26	11 (42.3%)	42

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BRUCELLOSIS IN PEDIATRIC PATIENTS: A REVIEW OF 114 CASES FROM ASIR REGION

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تم خلال أربع سنوات ادخال ١١٤ طفلا (تتراوح أعمارهم بين < ٢٨ يوما و ≤ ١٢ عاما) إلى مستشفى خميس مشيط المدني ولديهم إيجابية مصلية لداء البروسيلات. ويمثل هذا العدد ما نسبته ١٪ من جميع الأطفال الذين ادخلوا المستشفى. أظهرت القصة المرضية وجود احتكاك بالحيوانات الأليفة وشرب الحليب غير المغلي. وكان أكثر من ٨٤٪ من المرضى من المناطق الريفية في عسير. كانت نسبة الذكور إلى الإناث ١ر٢ : ١، وكان أكثر من ٥٩٪ منهم في سن الخامسة أو دونها. شوهدت أكثر الملامح السريرية تواردا كما يلي: الحمى (٨٠ر٧٪)، تضخم الكبد والطحال (٣٨٪)، اعتلال المفاصل (٢٩٪)، فقر الدم (٣٤٪). وكان أكثر من ٣٦٪ منهم يعانون من نقص التغذية. وأظهر التعيين المصلي للعوامل الممرضة وجود نوعي المالطية والمجهضة في (٥٣ر٥٪)، المجهضة فقط في (٣٢ر٥٪) والمالطية في (١٤٪)، وقد تلقى جميع الأطفال المرضى علاجا مركبا من «ريفمبيسين» و«سيبترين». ولم تحدث أية وفيات، فيما لوحظت إصابة طفلين بالتهاب الكبد نتيجة للعلاج. ويبدو أن داء البروسيلات هو أحد الأسباب الرئيسية لمراضة الأطفال في منطقة عسير وهناك حاجة ملحة لتطبيق برنامج فعال للسيطرة عليه.

Over a period of four years, 114 children (> 28 days to ≤ 12 years) with seropositive brucellosis were admitted to Khamis Mushayt Civil Hospital, constituting 1% of all pediatric admissions. History of contact with domestic animals and ingestion of raw milk was positive, and over 84% of the patients were from the rural areas of Asir. The male:female ratio was 1.2:1, over 59% were of ≤ 5 years of age. Common clinical features observed were fever (80.7%), hepatosplemomegaly (38%), arthropathies (29%), and anemia (34%). Over 36% of the children were undernourished. Serological identification of etiological agents revealed Abortus and melitensis (53.5%), Abortus (32.5%) and melitensis (14%). All patients were treated with a combination of rifampicin and septrin. There were no deaths, drug-induced hepatitis was observed in two cases. It would appear that brucellosis is one of the major causes of morbidity in the pediatric population located in the Asir region and there is an urgent need for an effective control program.

Brucellosis is one of the major health problems in both rural and urban Saudi Arabia [1]. While the epidemiology of the disease in the adult population is well documented [2,3], there is a paucity of data on its clinical pattern in Saudi children. This retrospective study was undertaken to evaluate the magnitude of the problem and to analyze the factors related to its clinical presentation in a selected population of pediatric patients requiring hospitalization in a district general hospital in the Asir Province of Saudi Arabia.

Material and Methods

Case records of all children (> 28 days to ≤ 12 years) with seropositive diagnosis of brucellosis admitted to Khamis Mushayt Civil Hospital over a period of four years (1406H to 1409H) were reviewed. Clinical laboratory, radiological and histological materials were reviewed and the diagnosis was verified or revised in each case. Of a total of 10,973 pediatric admissions, 114 children were identified to have a brucella agglutination titer ≥ 1:160. The serological diagnosis of brucellosis was made by collecting 5 cc of blood from each patient and the sera subjected to the slide

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agglutination test and tube agglutination test using gamma antigen preparation (Gamma Biologicals Inc., Houston, Texas, USA). A double dilution of serum from 1:10 to 1:2560 in tube method and 1:20 to 1:360 in slide method were used for the agglutination test. The tubes were incubated at 37°C for 48 hours. Positive and negative control sera were used for each batch of tests; against both strains of Brucella (*B. abortus* and *B. melitensis)* a significant titer of 1:160 was considered as positive for brucellosis.

For bacteriological isolation of brucella organism, blood cultures using tryptic soy broth and CO_2 under vacuum (Difco Laboratories, Houston, Texas, USA) were used; standard methods [4] for incubation, subcultures, bacterial identification and antibiotic sensitivity testing procedures were employed.

Results

Of a total of 114 cases, 67 were male (58.8%), there were only two cases of non-Saudi nationality. The majority of the patients (84.2%) were from the rural areas of the Asir Province with clustering of cases from Al-Farsha Tihama. Over 59% of the cases were of age group ≤ five years (Figure 1). History of contact with animals and ingestion of raw milk was present in all cases. Major clinical features are summarized in Table 1. History of anorexia and/or recent weight loss was present in only 2.6% of the cases. Causative organisms identified on serological examination were *B. abortus* and *B. melitensis* 61 (53.5%), *B. abortus* 37 (32.5%) and *B. melitensis* 16 (14%). Blood cultures were positive for the same organism in only one fourth of the cases, all the subjects with positive blood culture had an agglutination titer of > 1:160. Associated diseases were present in six cases (kala-azar four, malaria two). All cases were treated with a combination of septrin (trimethoprim 7 to 10 mg/kg/d, sulfamethoxazole 30 to 50 mg/kg/d) and rifampicin (20 mg/kg/d). Average duration of treatment was three to six weeks (mean 24.8 ± 4.6 days), longer duration being given to children with severe disease and/or arthritis (N = 33). Two infants developed drug-induced hepatitis requiring temporary discontinuation of therapy and two children developed recurrence of illness following complete recovery requiring a further course of treatment. There were no deaths.

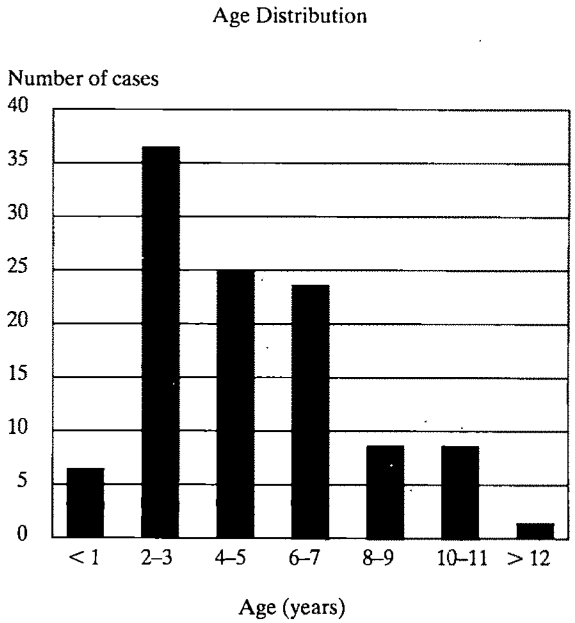

FIGURE 1. Age distribution.

TABLE 1. *Clinical features (N* = 114).

	N(%)
Fever	94 (82.4)
Hepatosplenomegaly	44 (38)
Arthralgia/arthritis	40 (35)
Undernutrition (Wt < 10 c)	42 (36.8)
Anemia (Hb < 10 g%)	39 (34.2)

Discussion

In most published reports from various centers in Saudi Arabia, the number of children with brucellosis ranges from 5% to 14% [1,3,5]. Our study demonstrates that brucellosis constitutes over 1% of all post-neonatal childhood hospital admissions reflecting the magnitude of the problem. Positive history of ingestion of raw milk in all our cases is perhaps more related to the preponderance of our patients from rural areas [1,6]. In contrast to adults we were unable to demonstrate any significant difference between the two sexes [1,3]. A significant degree of malnutrition has been reported to be present in about 12% to 14% of less privileged urban and 12% to 41% of rural preschool children of Saudi Arabia [7,8]. Over one-third of the patients were subcentile in their weight suggesting a significant recent weight loss and/or presence of a pre-illness state of undernutrition; an association between undernutrition and infection susceptibility in children is well known [6]. Over 59% of our patients, in whom milk is an important part of their diet, were ≤ five years of age. Hence, ingestion of raw milk puts them at a greater risk for acquiring the disease.

Brucellosis is a multi-system disease [9] and clinical presentation in children is mainly in the form of fever, arthropathies, visceromegaly and anemia [10,11]. By far, the most common presentation was pyrexia of unknown origin. We were unable to demonstrate overt central nervous system or cardiac manifestations in any of the cases but subclinical forms cannot be ruled out [12]. The presence of other associated disorders as malaria and kala-azar [13] should be searched for in all cases. Treatment of childhood brucellosis with a combination of septrin and rifampicin seems encouraging [14,15] with a need for regular monitoring of liver function test. Attention must be paid to the correction of undernutrition and anemia and to the health education of parents. Brucellosis is a preventable disease, and in view of the magnitude of the problem in children, there is an urgent need for an effective control program.

Acknowledgments

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SUBSTANCE ABUSE AMONG PATIENTS ATTENDING A PSYCHIATRIC HOSPITAL IN JEDDAH: A DESCRIPTIVE STUDY

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أجريت مراجعة دقيقة للملفات جميع مراجعي العيادات الخارجية لمستشفى تم افتتاحه مؤخرًا في جدة للعناية العاجلة بالحالات النفسية. تعرفت الدراسة على ٤٨٥ حالة لإساءة استعمال المواد على مدى سنة واحدة. كان الهيروين والكحول أكثر المواد التي أسيء استعمالها. أجريت مقارنة بين مرضانا وثلاث دراسات مماثلة من البلدان الغربية من حيث تاريخ العقار والخصائص الاجتماعية السكانية واتضح وجود بعض الفروق الهامة منها انخفاض نسبة الإناث والفرق الهام في فئة العمر بالاضافة إلى ارتفاع مقدار ما يتناوله المريض يوميًا بشكل عام.

A thorough retrospective review of all case notes of patients attending the outpatient clinics in a newly opened acute care psychiatric hospital in Jeddah identified 485 patients with substance abuse during a period of one year. Heroin and alcohol were the most common substances abused. Comparison of the drug history and sociodemographic characteristics of our patients with three similar studies from Western countries revealed some significant differences. Low female ratio, significant difference in age group, and generally higher daily regular intake are some of the differences.

Jeddah Psychiatric Hospital, an acute care psychiatric hospital, was opened in November 1988 and serves Jeddah city and the towns around it with a population of nearly 2 1/2 million. Saudi Arabia, having such a deep-seated religious social life, with its extended and close-knit families, has been reasonably protected from illicit drug use. Moreover, psychiatric disorders, particularly addictive behaviors are socially stigmatizing and tend to be concealed. This may explain the rarity of literature on this issue from this part of the world. Substance abuse and illicit drug experimenting have become one of the major public health problems in the recent years. The widespread increase in drugs prescribed, such as benzodiazepines, has undoubtedly led a few people to abuse them and/or becoming dependent on them, has been universal [1–4].

The definition of drug dependency or substance abuse has always posed difficulties and proved problematic. None of the current definitions provides a criteria which is objective or nonjudgmental that can be used for both diagnosis as well as for determining when to intervene or treat. For the purposes of this paper, substance abuse is defined as "the compulsive use of any psychoactive substance, illicit or prescribed, in enough and regular doses to such an extent that it adversely affects a person's health or socio-occupational functioning."

Our clinical impression in Saudi Arabia has been that subtance abuse as well as illicit drug use is not as uncommon as it seems. To assess the magnitude of the problem, we studied all case notes of substance abusers attending outpatient clinics in our hospital during a one year period (December 1988 to December 1989).

Method

During the period of study (December 1988 to December 1989) all case notes of patients attending our clinics were studied to identify substance abusers as defined above. Substance abusers were identified either by the history of abuse reported during the first interview or the diagnosis made by the treating psychiatrist. When interviewing new patients in the clinics, the staff routinely uses a standard medical format irrespective of the

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patients' condition. The data were collected from the case notes, independent of the medical staff who received and assessed the patients on first contact. In addition to medical records, relevant data were obtained from social workers and psychologists involved with these cases.

Results

A total of 17,254 males and 10,562 females attended the clinics during this period. Among these, only 485 patients were found to have substance abuse as their main problem. Using the main "problem" drug as the basis for classification, 211 patients (43.5%) were heroin addicts, 78 (16.1%) alcohol abusers, 71 (14.6%) polydrug abusers, 42 (8.7%) took benzodiazepines, 39 (8%) took barbiturates, 25 (5.2%) abused amphetamines and 19 patients took solvents, parnate and artane (8,6 and 5, respectively).

Only 13 patients (2.7%) were females. The mean age of the patients was 29.04 years (SD 8.67) with median age 27 years (range of ages was 15 to 65 years, with 26 patients (5.4%) younger than 20 years, 251 (51.8%) between 20 to 29 years, 192 (39.6%) between 30 to 45 years and only 16 (3.3%) older than 45 years).

Although 170 patients (35%) were referred by the police, only 24 (4.9%) of the sample were found to have a criminal record. The following detailed description is restricted to the vast majority of our patients who abused heroin and alcohol.

Heroin Use: Among the 211 heroin users, 11 patients (5.2%) were females, 68 (32.2%) were married, 126 (59.7%) were single, 17 (8.1%) divorced, 101 (47.9%) unemployed, 64 (30.3%) were over 30 years of age and only 17 (8.1%) were younger than 20 years; the mean age of starting heroin use was 23 years and 36 patients (17%) of the sample used other substances.

In view of the wide variations in the purity of street heroin, the daily amount consumed is best assessed by cost rather than weight [5]. The daily cost varied from less than 200 Saudi Riyals (SR) to more than 1200 SR which is equivalent to less than one gram to more than three grams by weight. A one gram bag of heroin in Jeddah ranges from 200 to 400 SR. Only 18% used less than one gram per day, 46% used about one gram per day, and 36% used two to three grams a day.

The most common routes of administration were: intravenous (IV) line only (37%); mainly sniffing, but with occasional IV injections (28%); sniffing only (23%), and smoking 12%. A total of 56% tried the IV injections at least occasionally, making this the most common route among our patients. The main reasons for starting drug use were: curiosity and peer group influence (58%); travelling abroad, mostly to the Far East (39%); and psychiatric disturbance (3%).

Alcohol Abuse: All 78 alcohol abusers were male. The mean age at which alcohol became a problem was 28.6 years (range 23 to 65 years) with a mean duration of 8.8 years (range less than one year to more than 30 years). Of these 78 patients, 42 (53.8%) were married, 13 (16.7%) single, 23 (29.5%) divorced, 13 (16.7%) unemployed; 43 (55%) were older than 30 years of age, none younger than 20 years. Fifteen (19%) had morning drinks to combat withdrawal symptoms while the remaining 63 (81%) took it only at night on a regular basis (regular drinking defined as every night).

The main reasons for alcohol abuse were: sociopsychological difficulties, mostly insomnia, social phobia and anxiety state (52.6%), peer group influence and travelling abroad (35.9%), and 11.5% failed to give any reason.

In comparing the sociodemographic characteristics of heroin users with those of alcohol abusers some significant differences came to light. The marital status differed significantly. While there were more single people among heroin users, there were more divorced persons among alcohol abusers. This difference reached statistical significance ($\times^2_{(2)} = 43.30$, $P < 0.01$); unemployment was significantly ($\times^2_{(1)} = 23.21$, $P < 0.01$) higher among heroin users; history of taking other substances was higher among alcohol abusers ($\times^2_{(1)} = 20.86$, $P < 0.01$) (Table 1). These differences indicate that both substances may differ in their adverse effects on individuals.

Discussion

To the best of my knowledge, this is the first paper from Saudi Arabia which has dealt with substance abuse. The data in this study are derived from attendants of outpatient clinics in a newly opened acute care general psychiatric hospital, so only limited conclusions can be drawn.

The vast majority of our sample were heroin and alcohol abusers (80.8%), a finding which is consistent with similar studies. However, comparison of sociodemographic characteristics in both groups showed significant differences (Table 1). These differences are difficult to attribute to the difference in age groups or the relatively long history of alcohol abuse in comparison to the recent and short history of heroin addiction in Saudi Arabia. We think this may be due to a better tolerance of the society to alcohol abuse compared to heroin use, though both substances are equally forbidden in Islam.

When we compared our results with those from three similar studies from Western countries (Table 2), the following differences come to light: (a) *Sex and Age*—our study has a very low female:male ratio, only 2.7% of the total sample and 4.3% of heroin addicts. In most studies from Western countries it varied between 28% to 40% [5–7]. We think this ratio may be similar to the ratio in those countries 20 to 30 years ago, so we must look for the underlying causes as well as for ways to prevent increased use in women. Among heroin addicts, patients under 20 years of age constituted only 8.2% of our sample. This contrasts with 15% to 50% in Western studies. We think this age difference is due to the extended and close-knit families which provide close supervision of members, in particular to the youngsters who do not usually obtain full autonomy until they are in their mid-twenties; (b) *Drug Preference and Addictive Attitude*—the best comparison can be made with the O'Rourke and Taylor study [5] (Table 3), since their study and our study described the characteristics of heroin users. Daily regular intake of heroin has been generally higher among our patients. Eighty-two percent of our patients were taking more than 1 gram/day compared to 83% of patients in O'Rourke and Taylor study [5] who took less than ½ gram/day. This difference cannot be explained by a higher tolerance among our patients nor by their wealth. We believe the explanation may be due to the difference in the purity of street heroin available in the Kingdom. Indeed, in the Eastern Province the purity of heroin was found not exceeding 4% (ac-

TABLE 1. *Sociodemographic differences between heroin and alcohol users.*

Drug	No. of patients	Married (no. of patients) (%)	Single (no. of patients) (%)	Divorced (no. of patients) (%)	Unemployed (no. of patients) (%)	History of other substances
Heroin	211	68 (32.2)	126 (59.7)	17 (8.1)	101 (47.9)	36 (17.1)
Alcohol	78	43 (55.1)	12 (15.4)	23 (29.5)	12 (15.4)	33 (43.3)

TABLE 2. *Comparison between four studies.*

Attributes	Fraser & Leigton 1984 [8]	Drummond et al 1986 [9]	O'Rourke & Taylor 1987 [5]	Present study
Number of patients	80	63	145	255
Self-referred	–	39%	40	67.1%
Mean age of first contact years	25.1	21.8	22.6	26
Range of age	19–55	–	15–35	16–65
Married	48%	–	16%	32.3%
Single	45%	75%	74%	59.9%
Divorced	7%	–	10%	7.8%
Unemployed	70%	83%	82%	47.8%
Criminal convictions	69%	42%	66%	9.4%
Current illegal activities	30%	27%	84%	5.9%
Mean duration of drug use	3.89	2.04	3.8	2.6

TABLE 3. *Comparison between heroin addicts in two similar studies.*

Attributes	Rourke & Taylor (N = 145)	Present study (N = 255)	Statistical values
Mean age at first contact	22.6 years	26.2 years	$t = 4.57$ $P < 0.01$
Younger than 21 years	51% (74)	9.9% (25)	$\chi^2_{(1)} = 84.37$ $P < 0.01$
Males	72% (104)	95.7% (244)	$\chi^2_{(1)} = 46.93$ $P < 0.01$
Unemployed	82% (119)	47.8% (122)	$\chi^2_{(1)} = 39.68$ $P < 0.01$
Marital state			
Married	16% (23)	32% (82)	
Single	74% (107)	60% (153)	$\chi^2_{(2)} = 12.72$ $P < 0.05$
Divorced	10% (15)	8% (20)	
Mean duration of drug use	3.8 years	2.6 years	
Regular daily intake			
Less than ½ gram	83% (120)	none	
Less than 1 gram	13% (19)	18% (46)	$\chi^2_{(2)} = 316.58$ $P < 0.01$
More than 1 gram	4% (6)	82% (209)	
Most common method of administration			
Injection	73% (106)	65% (166)	
Inhalation	14% (20)	23% (59)	$\chi^2_{(2)} = 5.09$ $P > 0.05$
Other routes	13% (19)	12% (30)	
Criminal conviction	66% (96)	9.4% (24)	$\chi^2_{(1)} = 135.48$ $P > 0.01$

cording to forensic evidence), a result which is compatible with the high doses among our patients compared to doses reported from Western countries with purity of heroin available ranging from 8% to 20% [5]. The serious implication of this finding rests not only on the extra money our patients are spending but on their higher chance to sustain a lethal complication due to the added contaminants.

Although the majority of heroin users (82.7%) strongly preferred heroin over other substances, the benzodiazepines, barbiturates and alcohol abusers mostly abused drugs concurrently or interchangeably. Insomnia, social phobia and anxiety state were found to be the underlying causes for the abuse in 52% of these patient findings which is in keeping with other studies [10,11].

In our sample, barbiturate abuse was as common as benzodiazepine abuse which contrasts with the late large increase in benzodiazepine abuse with a corresponding decline in barbiturates found in other studies. We believe this may be due to the fact that barbiturates are abundant and easily available on the black market while benzodiazepines are not. This supports the speculation of availability being one of the factors associated with causation. Almost all benzodiazepine abusers obtained them through official channels. The introduction of the new legislation which controls the prescription of all psychotropic drugs is expected to minimize this risk significantly.

In this sample, amphetamine and amphetamine-like substance abuse is not common while cocaine was virtually unknown. This may be due to the lack of availability in the market or the motive behind addictive behavior may be the narcotic and sedative effects, rather than elation and stimulation. This speculation, which may have some sociocultural implications, requires further evidence.

Association Between Drug Taking and Criminal Behavior

Although 170 patients (35.05%) of the sample were referred by the police, either after being convicted or awaiting trial, only 24 (4.9%) had a history of being charged with criminal behavior, mostly shoplifting and other forms of theft. Illegal possession of illicit drugs was the charge against all the others. We think this low percentage (4.9%) in contrast to Western studies (42% to 69%) may be due to either the wealth of our patients which enables them to finance their habit or due to an actual low criminality in their personality development. While the former is supporting the theory of criminality being an adverse effect of addiction, the latter is in keeping with criminality being and integral part of addictive personality development, and that addicts were criminals even before their addiction [12–16]. However, this general lower criminality in our patients, whatever the reason may be, may raise the possibility of addictive behavior being of a more benign nature presumably with a better prognosis in this country. This speculation needs more studies for confirmation.

The rarity of literature on substance abuse from developing countries seems not to reflect an actual low incidence. Our results are comparable to those from similar studies from Western countries. However, the few but significant differences which have come to light merit serious consideration and the role of sociocultural factors in causation of substance abuse and its course needs further well controlled studies from the developing countries.

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SCHISTOSOMIASIS MANSONI IN YEMEN: A REVIEW

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يعتبر داء المنشقات مشكلة صحية عامة في اليمن. وقد تم الابلاغ عن الاصابة بداء المنشقات المنسونية بين المرضى اليمنيين لأول مرة في عام ١٩٢٢م. وفي عام ١٩٥١م أجري أول مسح سكاني في تعز وأظهر وجود قواقع *BIOMPHALARIA BIOSSYI ARABICA* حيث كانت ما نسبته ٣٥٪ منها مصابة بشدة بداء المنشقات المنسونية فيما لم تظهر أية اصابة لدى الحلزون في صنعاء. وعلى الرغم من اكتشاف داء المنشقات المنسونية و داء المنشقات الدموية في معظم أنحاء الجمهورية العربية اليمنية، إلا أن هذا الداء لا يمثل فيما يبدو مشكلة الإصابة بداء المنشقات المنسونية وداء المنشقات الدموية في اليمن إلى هجرة المصابين باستمرار من إريتريا وغيرها من بلدان شرق أفريقيا. وتعد نسبة انتشار هذا الداء في المناطق الريفية أعلى منها في المناطق المدنية. أصبحت المضاعفات الناجمة عن داء المنشقات المنسونية وخصوصا ارتفاع الضغط البابي ودوالي المريء في الدم تمثل مشكلة سريرية رئيسية. إن توفر عقار «برازيكوانتيل» كعلاج مأمون وفعال يجعل اكتشاف الإصابات ومعالجتها جزءًا هاما من وسائل السيطرة على داء المنشقات. وتتطلب السيطرة على هذا الداء أيضا القيام بدراسات ميدانية، يتبعها رش مبيدات الرخويات وتطوير مصادر المياه والصرف الصحي، وأخيراً وهو الأهم، توفير التعليم الصحي.

Schistosomiasis is a major public health problem in Yemen. In 1922 *Schistosoma mansoni* was first reported to be found in Yemeni patients. In 1951 the first population survey was carried out in Taiz and revealed the presence of *Biomphalaria biossyi arabica* where 35% of the snails were heavily infected with *S. mansoni* and in San'a no snails were infected. Although *S. mansoni* and *S. hematobium* infections have been found in most parts of the Yemen Arab Republic (YAR) it seems that the disease is not a public health problem in some parts of the country such as Hodeidah, Al-Beidah, Mareb, and Al-Gouff. The source of *S. mansoni* and *S. hematobium* in Yemen was attributed to the continual migration of infected persons from Eritrea and other countries of East Africa to Yemen. The prevalence of infection is higher in rural than in urban areas. The complications of *S. mansoni*, notably portal hypertension, esophageal varices, and hematemesis have become a major clinical problem. The availability of Praziquantel as a safe and effective treatment makes case finding and treatment an important part of schistosomiasis control. Control of the disease also requires field studies followed by molluscicíding, improvement of water supply and sanitation and, perhaps most importantly, health education.

In 1922, Greval [1] first reported the presence of *Schistosoma mansoni* in two Yemeni patients in a hospital located in Aden, South Yemen. One patient was from Usaifira, North Taiz, and the other from Makatrira, West Taiz. In 1951, the first surveys were carried out when the United States Naval Medical Research Unit No. 3 (NAMRU3) examined snails taken from three different locations: (a) San'a, 7,200 feet above sea level, (b) Taiz, 4,100 feet and (c) Hodeidah on the Red Sea coast. In Taiz, the survey revealed the presence of *Biomphalaria biossyi arabica* of which 35% of the snails examined were heavily infected with *S. mansoni*. In San'a, *Biomphalaria* spp. were not infected and in Hodeidah, no snails were found. However, few infections among the population were found in the last two cities.

The source of *S. mansoni* and *S. hematobium* in Yemen was attributed to the continual migration

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of infected persons from Eritrea and other countries of East Africa to Yemen [3]. Kuntz et al [3] found that the majority of patients infected with *S. mansoni* in San'a and Hodeidah had come from Taiz. To investigate the presence of helmenthic infection, fecal and urine specimens were obtained from 218 persons living in Taiz which revealed 56% *S. mansoni*.

Between December 1951 and February 1952 [4] a small study carried out in three public schools in San'a, Taiz and Hodeidah showed that in Taiz, 14 of 20 stools examined for *S. mansoni* ova were positive (70%). All the infected people came to Taiz from surrounding regions. The individuals included in this study were a mixture from primary, secondary, and orphanage schools as well as adult staff between the ages of 9 to 35 years. However, in San'a and Hodeidah, *S. mansoni* infection was much less frequent than in Taiz.

In 1972, Arfaa [6] showed schistosomiasis as being one of the most important public health problems in Yemen. He estimated the total number of people in Yemen infected with *S. mansoni* and/or *S. hematobium* to be more than one million out of a total population of 5 to 6 million [6]. The southern parts of Yemen Arab Republic showed the highest prevalence of *S. hematobium* while both species were found in a patchy distribution in all areas visited except Hodeidah. In Hajjah, North San'a, the prevalence of *S. hematobium* was found to be much greater than the prevalence of *S. mansoni* (76% and 15% respectively), while in Hujariah and Rahidah, South Taiz, the prevalence of *S. mansoni* was more than that of *S. hematobium* (40% and 30%, respectively).

Warren et al [7] reported the endemnicity of *S. mansoni* in Yemeni immigrants living in the San Joaquin Valley in California, USA. Two hundred eighteen Yemeni workers were investigated and 56% were positive for *S. mansoni*. The life span of the Yemeni strains of *S. mansoni* was estimated to be five to ten years.

The effect of *S. mansoni* infection on the liver and spleen was reported by Mount [5] in 1953. In Taiz, 76 (38.2%) people under 21 years had hepatomegaly and 60.6% in the same group had splenomegaly (Table 1).

TABLE 1. *Effects of S. mansoni infection on the liver and the spleen of Yemeni patients in 1951.*

City	No. of patients examined	No. of patients with hepatomegaly	No. of patients with splenomegaly
Taiz	76	29 (38.2%)	46 (60.6%)
San'a	54	1 (1.8%)	2 (3.7%)
Hodeidah	129	9 (6.9%)	19 (14.7%)
Total	259	39 (15%)	67 (25.8%)

A combined Yemen/WHO project set up in 1973 to control schistosomiasis in Yemen, reported the presence of *S. mansoni* and *S. hematobium* in most parts of the YAR and estimated that 25% of the population were infected with one or both species [8,9]. A malacological survey showed that *Biomphalaria,* the snail intermediate host of *S. mansoni,* is common in Taiz and Ibb. In 1988, surveys [8] showed that both species of schistosome were found in San'a, Saada, and Hajja. Both species were found to be endemic in Taiz, Ibb, Thamaar, and Al-Mahweet with *S. mansoni* being the most common. It seems, however, that the disease is not a public health problem in other parts of the country such as Hodeidah, Al-Beidah, Mareb and Al-Gouff.

Schistosomal hepatofibrosis with consequent portal hypertension and esophageal varices with a high risk of hematemesis is a major clinical problem in Yemen. Between 1985 and 1988, during work being done in the Department of Medicine and in the Gastrointestinal Endoscopy Unit in Al-Thawra Modern General Hospital, it was found that severe upper gastrointestinal bleeding from ruptured esophageal varices was a common problem. Although the patients who were investigated about the cause of the esophageal bleeding gave a history of *S. mansoni* infection, one cannot be certain whether this bleeding is due to schistosomal hepatofibrosis or due to hepatitis B related cirrhosis which is also common in Yemen [11]. A further study to find out the definitive cause of the esophageal varices is indicated.

Conclusion and Recommendations

Schistosomiasis caused by *S. mansoni* as well as *S. hematobium* is a major public health problem in Yemen. Epidemiologically, the prevalence of infection is higher in rural than in urban areas, due mostly to the improvement of water supplies to urban areas. The size of the problem is likely to become more prominent considering that more than 90% of the population of YAR live in the rural areas. Schemes to control the spread of *Schistosomiasis* involve case findings and treatment, control of snail intermediate hosts, improvement of water supplies, prevention of contact with snail-infested water and, perhaps most importantly, health education. In 1983 [8] Praziquantel (Biltricide) was introduced into the control scheme. Praziquantel is distributed free of charge by the project staff to patients proved to be positive for schistosomiasis. The availability of praziquantel as a safe and effective chemotherapeutic agent makes case findings and treatment an important part of schistosomiasis control. Regular surveillance of communities, i.e., active case findings and treating infected persons will not only decrease the risk of developing schistosomal disease, but will rapidly decrease the intensity and prevalence of infection [10]. Continuous molluscicciding of water sources of suspected areas has been found to be very effective according to the WHO report on schistosome infected snails in the area surrounding the Mareb Dam (northeast YAR). In 1988, this area was found to be free of snails after using molluscicides in 1987 when both *Biomphalaria* and *Bulinus* snails were found in large numbers. Other methods of snail control include elimination of pools, removal of vegetation, prevention of pollution, increasing the rate of water flow and changing the level of water in dams [10]. Improvement of water supplies that have taken place in recent years will also help to reduce the risk of infection. Finally, health education and health promotion are of major importance in the control of schistosomiasis in Yemen.

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COMPLICATIONS OF PRIMARY UPPER GASTROINTESTINAL LYMPHOMA

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تتناول هذه الدراسة الورم اللمفي الابتدائي في أعلى الجهاز الهضمي والمضاعفات المرتبطة به. حدثت المضاعفات لدى واحد وعشرين مريضا «بنسبة ٦٤٪» من بين ٣٣ مصابين بهذا الورم، شملت الاختلاطات نزفا في أعلى الجهاز الهضمي لدى ١١ مريضا، وتضيقا في لمعة الجهاز الهضمي لدى ٩ مرضى، وسوء الامتصاص لدى ٥ مرضى ويرقانا انسداديا لدى أربعة مرضى. حدثت حالة ثقب لمريض واحد وتشكل ناسور لدى مريض آخر. عولج ممن أصابتهم المضاعفات معالجة كيميائية فقط ١٣ مريضا، وبالاشتراك مع إجراء جراحي ٦ مرضى أو بالاشتراك بين العملية الجراحية والمعالجة بالأشعة مريضين (٢). حدثت حالة وفاة واحدة بين أربعة مرضى نتيجة لمضاعفات الجهاز الهضمي بسبب نزف شديد في أعلى الجهاز الهضمي، أما الثلاثة الآخرون فقد توفوا بسبب انتان دموي عصي على العلاج. خلاصة القول، يعاني جمهور دراستنا من المصابين بالورم اللمفي الابتدائي في أعلى الجهاز الهضمي من معدلات مرتفعة للمضاعفات في الجهاز الهضمي. لم تكن معدلات الوفيات بصفة عامة مرتبطة بمضاعفات الجهاز الهضمي.

This study reports the gastrointestinal complications of primary upper gastrointestinal lymphoma (PUGIL). Of thirty-three patients with PUGIL, twenty-one (64%) had complications. These included upper gastrointestinal bleeding, narrowing of the lumen, malabsorption and obstructive jaundice in 11, 9, 5 and 4 patients, respectively. Perforation and fistula formation were encountered in one patient each. The patients with complications were treated with chemotherapy alone (13), in combination with surgery (6), or combination with surgery and radiotherapy (2). Only in one of four patients was the mortality due to gastrointestinal complication in the form of severe upper gastrointestinal hemorrhage. The remaining three patients died of refractory septicemia. In conclusion, there was a high rate of gastrointestinal complications in patients with PUGIL in our population. Mortality was commonly unrelated to these gastrointestinal complications.

Gastrointestinal lymphoma, mainly in the form of primary upper gastrointestinal lymphoma (PUGIL), represents one of the common forms of extranodal non-Hodgkin's lymphomas which is relatively common in the Middle East [1–5]. A few studies from Saudi Arabia have reported the clinicopathological features of this entity. Abdominal pain and weight loss are the most common presenting manifestations [6–8]. Complications of this disease are described in patients reported from the Western world [9–12]. These complications are primarily due to the disease itself or to its treatment and include perforation, jaundice, hemolysis and intestinal obstruction.

Although PUGIL is common in the Middle Eastern countries, there is little information on its complications in our population. Therefore, the present analysis was undertaken to report the frequency of gastrointestinal complications among 33 patients with PUGIL treated and followed at King Khalid University Hospital (KKUH), Riyadh.

Patients and Methods

Between 1405H and 1409H (1985 and 1989), thirty-

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three patients were diagnosed as having PUGIL (involving the stomach, duodenum and/or proximal jejunum) on the basis of histopathological features identified on examination of biopsy specimens. The clinical and laboratory features in some of these patients have been reported previously [8]. All patients were treated with chemotherapy alone or in combination with surgery and/or radiotherapy. The patients were followed at regular intervals over a period ranging from six to 60 months (median 1.87 years). During the follow-up visits, routine investigations including complete blood count, bilirubin, albumin, serum aspartate transaminase, serum alanine transaminase and alkaline phosphatase, electrolytes and urea, were obtained. Upper gastrointestinal (UGI) endoscopy was performed on all the patients at six month intervals during the follow-up, or earlier, if so indicated. Multiple biopsies were taken from both the grossly abnormal and normal mucosa of the fundus, corpus, antrum, first, second and third parts of the duodenum. These biopsy specimens were processed and examined microscopically. Blood and other body fluids were cultured if sepsis was suspected. Complications at presentation or during the follow-up period were diagnosed and managed accordingly. Upper gastrointestinal bleeding was diagnosed by the history of hematemesis and/or melena with endoscopic confirmation of bleeding sites within the UGI. The diagnosis of malabsorption was based on the occurrence of weight loss, steatorrhea, hypoproteinemia and abnormal D xylose test. Patients with recurrent vomiting and narrowing of the UGI lumen on endoscopic examination were deemed to have UGI obstruction. Obstructive jaundice was confirmed by ultrasound, computed tomographic (CT) scan and/or endoscopic retrograde cholangiopancreatography (ERCP).

Results

Gastrointestinal complications were documented in 21 of the 33 patients with PUGIL. Of the 21 patients with complications, 17 were male and 4 female. Their median age was 38.5 years. The disease was limited to the stomach in seven patients and ten to the duodenum and prox-imal jejunum. Another four patients had gastric, duodenal and proximal jejunal lymphoma which was associated with immunoproliferative small intestinal disease (IPSID) in three.

TABLE 1. *Gastrointestinal complications of primary upper gastrointestinal lymphoma (PUGIL).*

Complications	Frequency (%)*
Upper gastrointestinal bleeding	11 (52)
Acute	6
Chronic	5
Narrowing of the lumen	9 (43)
Gastric	3
Small intestinal	6
Malabsorption	5 (24)
Obstructive jaundice	4 (19)
Miscellaneous	2 (10)
Perforation	1
Fistula formation	1

* Some patients had two or three complications.

The most frequent complications were upper gastrointestinal bleeding and narrowing of the lumen in 11 and nine patients, respectively (Table 1). Malabsorption [5] and obstructive jaundice [4] were also frequent. The least common complications were perforation and fistula formation in one patient each. Some patients had more than one complication accounting for a total of 31 complications. Ten of these patients presented with gastrointestinal emergencies in the form of acute upper gastrointestinal hemorrhage in six, acute intestinal obstruction in one, free intestinal perforation in one and severe malabsorption with cachexia necessitating total parenteral nutrition in two patients. The vast majority of gastrointestinal complications occurred before the initiation of treatment. Only two patients developed complications in the form of hemorrhage and perforation within the first week of chemotherapy. None of the patients who underwent surgery followed by chemotherapy developed gastrointestinal complications. Mortality was encountered in four patients with malignant large-cell lymphoma of the small intestine. The mortality was due to gastrointestinal complication in only one patient in the form of severe upper gastrointestinal bleeding and three patients died with refractory septicemia.

Discussion

This study documents a relatively high gastrointestinal complication rate of 64% in patients with PUGIL. The most common complication was upper gastrointestinal hemorrhage which occurred in about half of these patients and was the cause of death in one. This frequency of bleeding was higher than the reported figures ranging from 15% to 30% in other populations [10]. Al-Bahrani et al [1] and Grey et al [10] reported intestinal obstruction as the most common presentation and complication. In contrast, we found acute intestinal obstruction in one patient only despite the presence of stenosis in 43% of our patients.

Obstructive jaundice was present in four patients in this series. The common bile duct obstruction was primarily distal due to lymphadenopathy, infiltration of the terminal bile duct and/or papilla of Vater. Birrer and Young [12] found obstruction of the bile duct most commonly at the porta hepatis or at the head of the pancreas due to enlargement of involved lymph nodes. They also reported that hepatocellular jaundice was infrequent despite hepatic involvement by small-cell non-Hodgkin's lymphoma. This type of jaundice was not recorded in any of our patients who had, in the vast majority, diffuse large-cell type of non-Hodgkin's lymphoma.

Although perforation has been considered as an important complication [9,11,13–15], only one of our patients suffered perforation following chemotherapy. Similarly, a blind duodenal fistula was present in one patient, a complication which has been reported infrequently.

Despite the occurrence of complications, the response to the different modalities of treatment mentioned above was fair. The mortality in one of our patients during the follow-up period was due to severe gastrointestinal bleeding, a potentially treatable condition. On the other hand, it has been reported that ten percent of patients surgically treated for non-Hodgkin's gastric lymphoma [11] died postoperatively. In the present series, none of our patients died during or after surgical intervention. However, the small number involved will not permit any firm conclusion on the morbidity and mortality of surgical treatment of PUGIL.

It is concluded that gastrointestinal complications of PUGIL are common and mostly not related to treatment. The majority of these are treatable conditions. Efforts should be made to identify and treat such complications in order to improve the prognosis of this entity. The prognosis of PUGIL is relatively fair and may depend mostly on the prompt arrest of complications usually due to chemotherapy.

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ENDOSCOPIC BILIARY DRAINAGE OF POSTOPERATIVE BILIARY FISTULAE AND LEAK

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تم بالتنظير الداخلي تشخيص خمس حالات متتابعة لنواسير صفراوية أو تسرب صفراوي عقب الجراحة ومعالجتها. ارتبط تكون النواسير بانسداد حصوي قاص في القناة الصفراوية لدى أربعة مرضى وبكيسة عدارية ثانوية لدى المريض الخامس. نجح بضع المصرة بالتنظير الداخلي مع استخراج الحصاة أو الكيسة في إزالة الضغط عن الجهاز الصفراوي وغلق النواسير. استخدم أنبوب صفراوي لدى مريضين واحتجنا لبديل صنعي داخلي لغلق الناسور لدى مريض آخر. يبدو أن المعالجة بالتنظير الداخلي في مثل هذه الحالات أفضل من تكرار التدخل الجراحي لإصلاح النواسير أو التسرب.

Five consecutive patients with postoperative biliary fistulae or leak were diagnosed and treated successfully by endoscopic intervention. The development of the fistulae were related to distal common bile duct obstruction by stones in four patients and in one patient by hydatid daughter cysts. Endoscopic sphincterotomy with stone or cyst extractions achieved decompression of the biliary system and initiated closure of the fistulae. In two patients, nasobiliary tube was used and endoscopic endoprosthesis was needed to close the fistula in another patient. In such cases, endoscopic management seems to be superior to surgical re-intervention for repair of fistulae or leak.

The development of biliary fistulae or leak may occasionally complicate surgical intervention on the biliary tree [1,2]. This can be caused by a retained bile duct stone causing obstruction of the common bile duct [1,2] or may also be secondary to bile duct injury or biliary stenosis. Fistulae may be complicated by infection which prevents healing. Corrective surgery is usually needed to relieve biliary fistulae [2]. Percutaneous transhepatic treatment has been attempted but it is accompanied by complications such as bleeding or it can be technically difficult to perform [3].

This is a report on five cases with postoperative biliary fistulae or leak which were related to retained bile duct stones in four and retained hydatid cysts in CBD in the fifth case.

Case Reports

Case 1: Biliary Abdominal Leak from Cystic Duct Stump with Retained Common Bile Duct Stones

A 63-year-old male previously underwent two operations in a local hospital for gallbladder disease. Due to a great deal of difficulty during surgery, the surgeon closed the patient without inserting a drainage tube. A few days after the second operation the patient's abdomen started collecting a large amount of fluid. Ascetic tap revealed bile in the abdomen. The patient was then referred to our hospital for further treatment. On admission he was ill, vomiting frequently, dehydrated and had septecemic shock for which he was rehydrated and treated with antibiotics. On examination, percutaneous abdominal drain was inserted in the right iliac fossa and four liters of infected bile was gradually drained over 48 hours and over 500 ml of bile continued to drain daily. Endoscopic retrograde cholangiopancreatography (ERCP) showed retained common bile duct stones and massive leak from the stump

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of the cystic duct (Figure 1A). Endoscopic sphincterotomy and stone extraction was performed. A nasobiliary tube was initially inserted but there was still massive bile leak in the abdomen (Figure 1B). ERCP was repeated and an internal endoprosthesis, placed above the cystic duct stump (Figure 1C), was left for a period of two months. The patient made a rapid and progressive improvement and the total parenteral nutrition (TPN) which was started initially was stopped as the patient was able to take his nutrition orally. ERCP two months later showed that the leak had closed completely (Figure 1D). Therefore, the endoprosthesis was removed and the patient was discharged from the hospital in good condition.

Case 2: Cystic Duck Leak with Cholangitis and Abscess Formation Secondary to Common Bile Duct Obstruction by Retained Stones

A 35-year-old female developed fever and jaundice a few days following cholecystectomy. Upper abdominal ultrasound showed localized fluid collection and no evidence of biliary tree dilatation. ERCP showed pus pouring out of the papilla, retained common bile duct stone obstructing the biliary tree and a localized leak from the cystic duct region (Figure 2A). Endoscopic sphincterotomy and stone extraction was performed and a nasobiliary drainage tube was inserted into the abscess cavity (Figure 2B). The patient made a substantial and quick recovery, and her jaundice and pyrexia disappeared a few days following intervention. The nasobiliary tube was left for 21 days for drainage of the infected leak after which it was removed and the leak closed completely (Figure 2C).

Case 3: Left Hepatic Duct Leak After Left Hepatectomy Caused by Impacted Stone in the Papilla with Obstruction of The Biliary Tree

A 50-year-old male with hepatoma of the left lobe of the liver underwent a left hepatectomy with a good recovery. Postoperatively, T-tube cholangiogram showed a left hepatic duct leak and the blocking of the distal common bile duct by a filling defect and left hepatic duct fistula (Figure 3A). ERCP showed a small stone impacted in the papilla of Vater (Figure 3B). Endoscopic sphincterotomy and stone extraction was performed and good drainage was achieved (Figure 3C). Two weeks later, the T-tube cholangiogram showed closure of the fistula with good drainage of the bile into the duodenum (Figure 3D).

Case 4: Biliary Leak From Common Hepatic Duct After Right Hepatectomy Caused by Retained Stone in Distal Common Bile Duct

A 50-year-old male developed right hypochondrial pain a few days following a right hepatectomy for metastasis. Ultrasound showed evidence of fluid collection in the hilum of the liver. ERCP showed a stone in the distal common bile duct with a biliary leak in the region of the common hepatic duct (Figure 4A). Endoscopic sphincterotomy and stone extraction were performed and the patient made progressive improvement (Figure 4B). Follow-up ultrasound and ERCP showed no further evidence of any fistula with good biliary drainage into the duodenum.

Case 5: Biliary Cutaneous Fistula After Removal of Liver Hydatid Cyst with Retained Daughter Cyst in the Common Bile Duct

A 65-year-old male presented with severe right hypochondrial pain, jaundice, and pyrexia. Ultrasound showed a large cyst in the liver with multiple daughter cysts. The patient was treated initially with antibiotics followed by laparotomy where a ruptured hydatid cyst into the biliary tree was found. Surgical evacuation of the main cyst was performed and irrigation with silver nitrate of the main cyst was done before attempt of complete evacuation of the biliary tree from daughter cyst. A T-tube was inserted in CBD and another tube was inserted in the large liver cyst. The patient made a slow postoperative recovery and there was evidence of bile leak from the cyst cavity and sinogram showed evidence of communication between the main cyst and the biliary tree. The cholangiogram also showed evidence of retained daughter cyst blocking the common bile duct (Figure 5A). ERCP, sphincterotomy and evacuation of the daughter cyst were performed and a nasobiliary tube was inserted to decompress the biliary tree (Figure 5B). This resulted in the clearing of the biliary tree from retained daughter cysts and closure of communication between biliary tree and the liver cyst cavity (Figure 5C). The patient

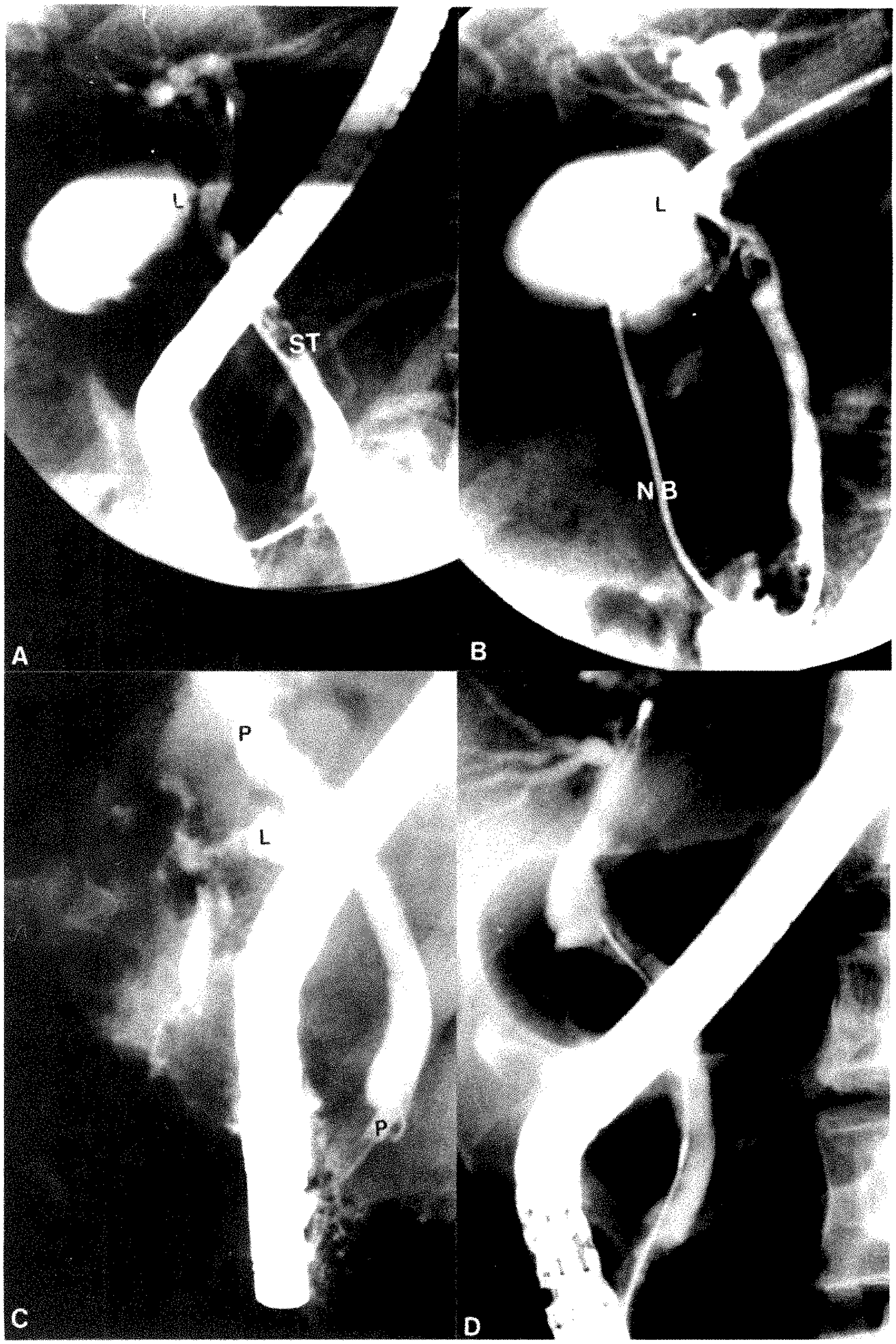

FIGURE 1. (A) Biliary leak from cystic duct stump (L), multiple stones in CBD (ST) basket in CBC, (B) in the same session nasiobiliary (NB) tube was inserted, (C) view of biliary endo-prosthesis (P) just after insertion. Leak from cystic duct still present (L), (D) ERCP after removal of the stent showing closure of the fistula.

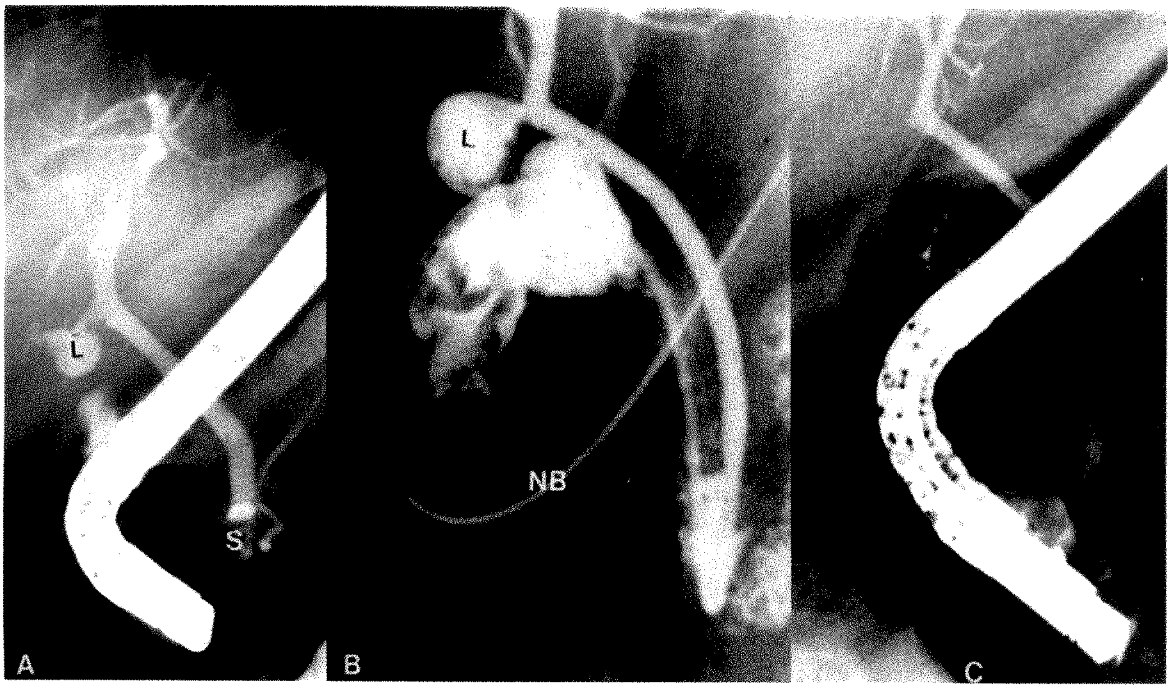

FIGURE 2. (A) Initial ERCP showing leak of cystic duct stump (L) and small stone in distal CBD (S), (B) nasobiliary drainage tube (NB) after insertion in infected leak site (L), (C) normal ERCP after closure of the leak three weeks later.

made a progressive substantial recovery and was discharged from the hospital in good condition.

Discussion

Biliary fistula occurring after surgical intervention on the biliary tree usually requires surgical reintervention [1,2]. Percutaneous transhepatic drainage has been attempted in the treatment of bile duct fistulae [3]. During the last few years, successful endoscopic management of postoperative biliary fistulae have been reported [4–10]. The majority of these cases have been associated with retained bile duct stones obstructing the distal biliary tree [2,3]. In four cases, there was evidence of bile duct stones obstructing the biliary tree. Retained daughter hydatid cysts of the common bile duct were found in the fifth case. A decompression of the biliary tree by endoscopic sphincterotomy and stone extraction is the main step to relieving obstruction and facilitating closure of the fistula or leak. In two of our patients, sphincterotomy with stone extraction alone resulted in closure of the fistula. The decompression alone may not be enough if the leak is very large, as noted in the first case, and an endoprosthesis is needed to bypass the leak temporarily. The optimum recommended duration of stenting using an endoprosthesis varies in different series. Ponchon et al [10] suggested four months and Huibregste et al [11] advocated replacement after three months and removal following six months. Endoprosthesis as noted in the first case was removed after two months as ERCP and filling through endoprosthesis showed no further biliary leak. Cholangitis and abscess formation at fistula site can further complicate the condition. Nasobiliary tube insertion in two of our patients facilitated drainage, disappearance of cholangitis and abscess as well as closure of the biliary leak.

In our patients, the closure of the fistulae was related to the size of the leakage only and not to the site of bile duct injury. Following decompression of the biliary tree, even the fistulas originating from proximal biliary tree closed rapidly.

We think that endoscopic intervention in biliary fistulae and leak should replace surgical repair as it deals with the main etiology for development of biliary fistula which in most of our cases was retained common bile duct stone and this reduced

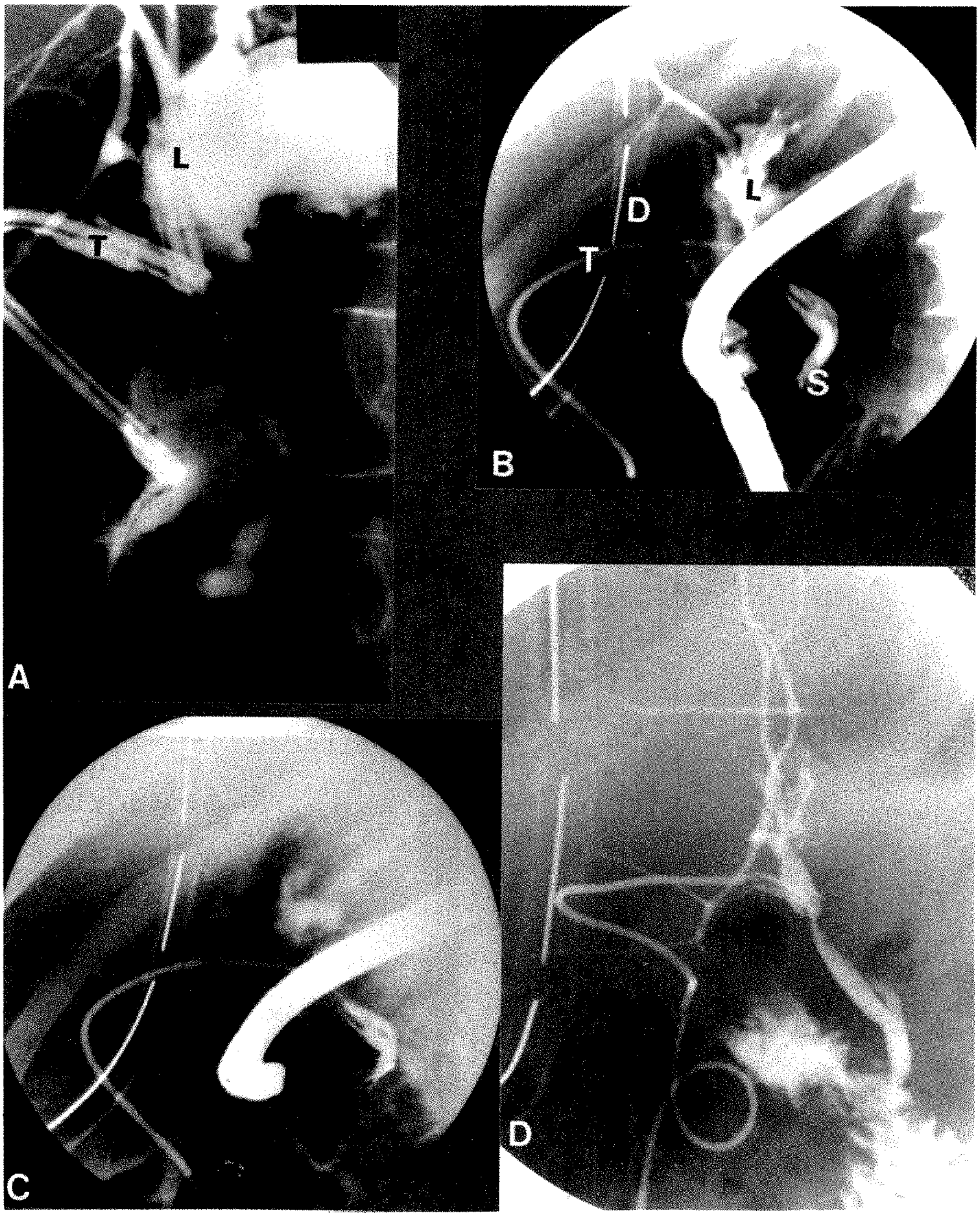

FIGURE 3. (A) T-tube cholangiogram showing leak of left he-patic duct (L), T-tube in situ (T) and surgical drainage tube (D); (B) ERCP confirming the leak (L) and stone (S) in distal CBD; (C) ERCP after removal of stone; (D) cholangiogram two weeks later showing closure of the fistula.

the morbidity and mortality of corrective surgery for repair of the fistula. In one of our cases, retained hydatid cysts which acted like a stone were extracted with decompression of the biliary tree. Stenting should be used in cases involving large biliary leak. Nasobiliary drainage facilitates good follow-up on the fistula situation and the possibility of repeated culture of the drained bile in cases of an accompanying infection.

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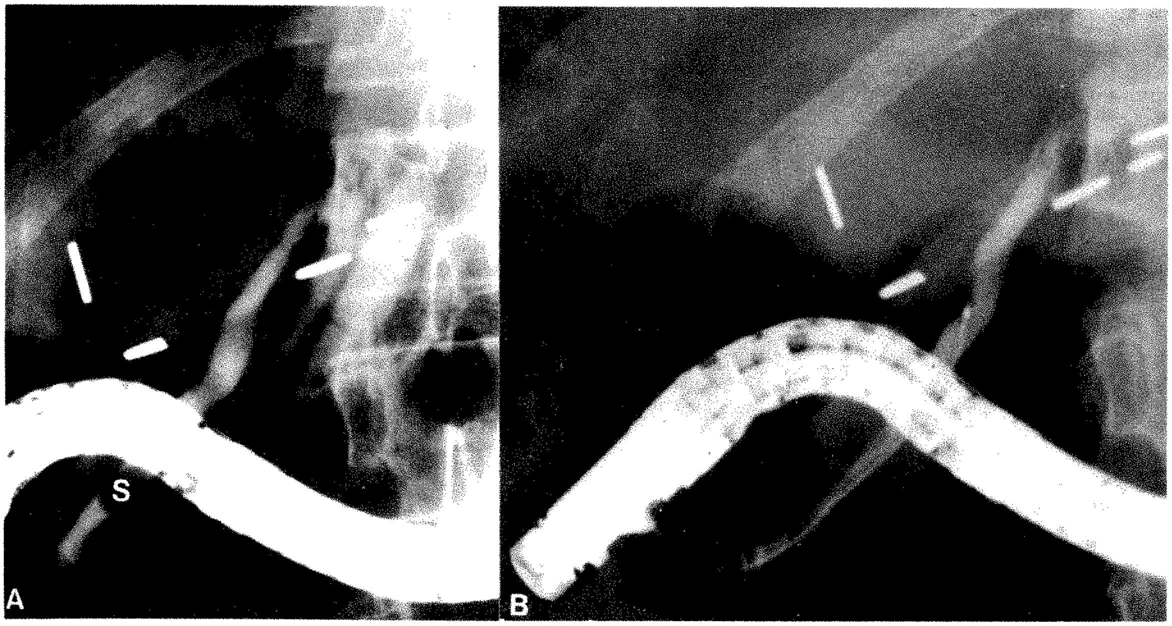

FIGURE 4. (A) ERCP showing stone (S) in distal CBD and leak from CHD (L). (B) ERCP after removal of the stone.

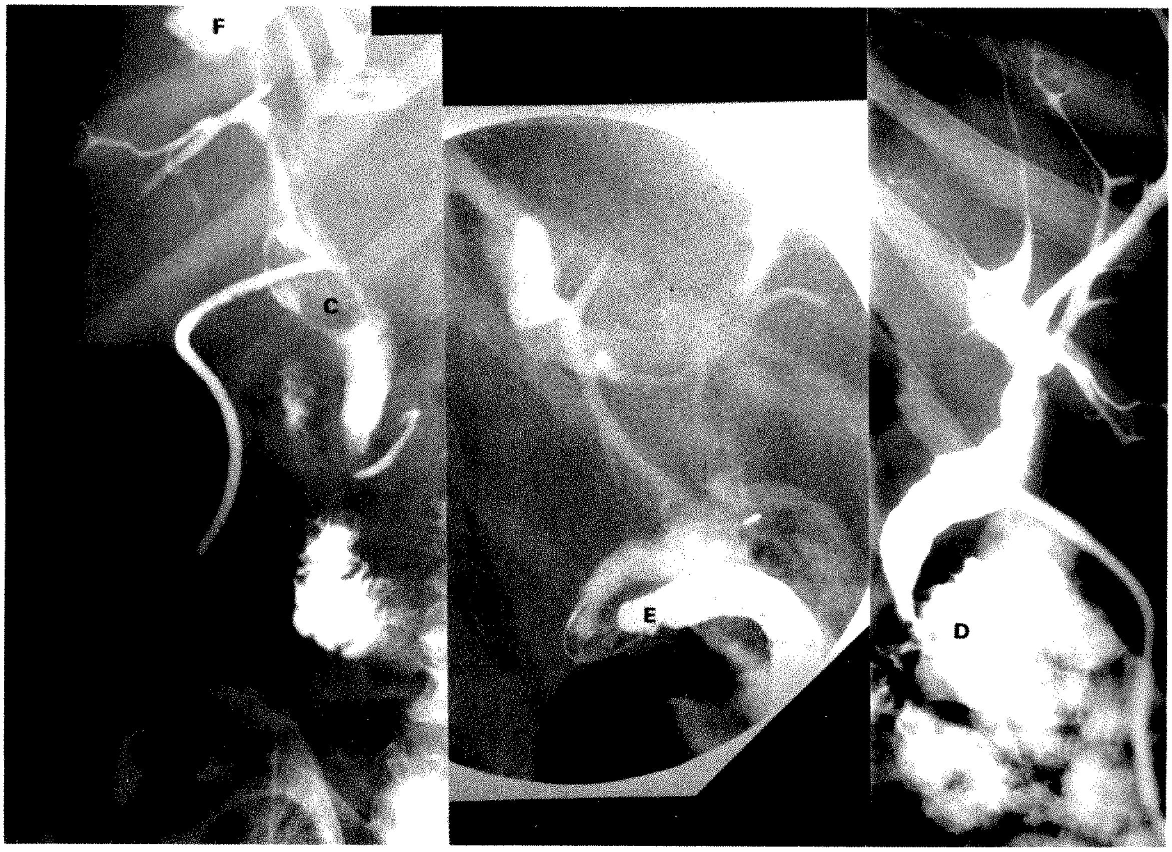

FIGURE 5. (A) T-tube cholangiogram showing obstruction of distal CBD by hydatid daughter cysts (C) with possible communication site to main cyst (F); (B) endoscopic removal of hydatid cysts after sphincterotomy. (E) endoscope; (C) nasobiliary cholangiogram showing clearing of the CBD and free drainage to duodenum (D).

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Case Reports

METASTATIC CHONDROSARCOMA OF THE BRAIN: A CASE REPORT

Ashraf Jallu, MS; Imaduddin Kanaan, MD; Shekhar Agarwal, MS

Primary intracranial mesenchymal chondrosarcoma is a well known entity. A metastatic tumor of this type is very rarely seen intracranially because the usual behavior of chondrosarcoma is local invasion or recurrence. The authors describe a patient in whom, eight months following removal of a chondrosarcoma of the femur, a metastatic lesion developed in the right occipital lobe of the brain.

Case Report

A 45-year-old female presented with a three-year history of pain in the left proximal thigh. Plain x-rays of the region showed an expansion of the proximal half of the femur with widening of the cortex (Figure 1). A bone scan showed an increased uptake in the femur. A biopsy was taken of the lesion and a diagnosis of grade II chondrosarcoma was made. A wide excision of the tumor and reconstruction of the femur was performed. The patient was discharged home in good condition and her initial follow-up remained satisfactory. She returned eight months later complaining of headache, visual disturbances, and bouts of vomiting. Clinical examination revealed a left homonymous hemianopsia. Computed tomography (CT) scan of the brain showed a ring-enhancing lesion in the right occipital area (Figure 2). This lesion was totally excised through a craniotomy. By histological examination the lesion was diagnosed as metastatic chondrosarcoma (Figure 3). The patient made a good recovery and was discharged home on the seventh postoperative day, free of symptoms.

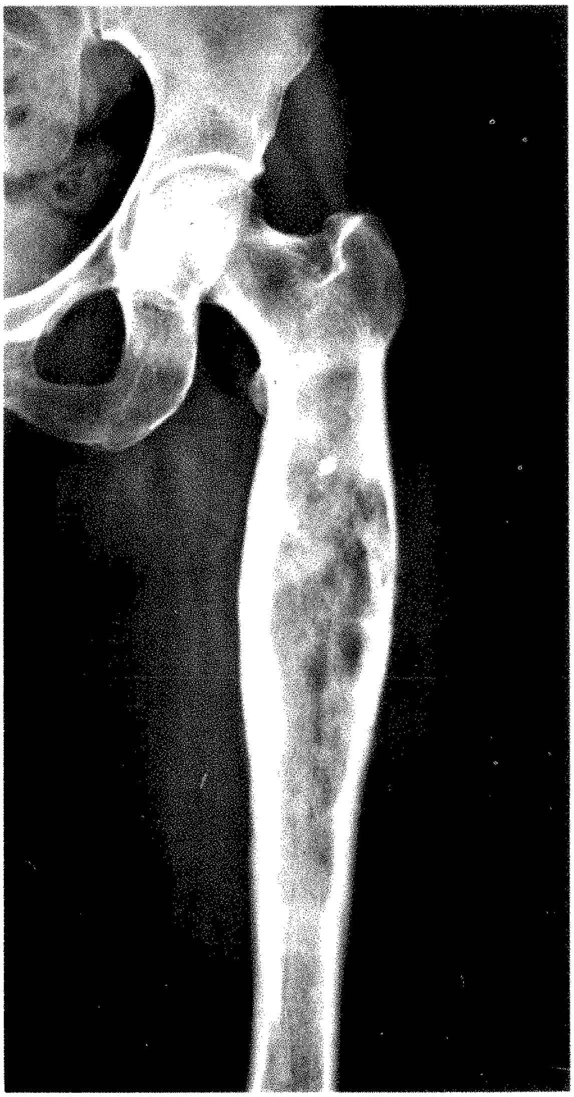

FIGURE 1. Plain x-ray of the femur, showing expansion of the proximal half with widening of the cortex.

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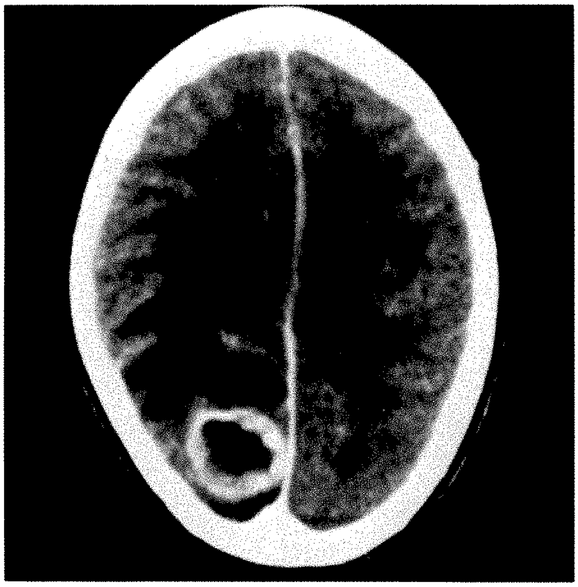

FIGURE 2. Computed tomography scan of the brain, showing a ring-enhancing right occipital lesion.

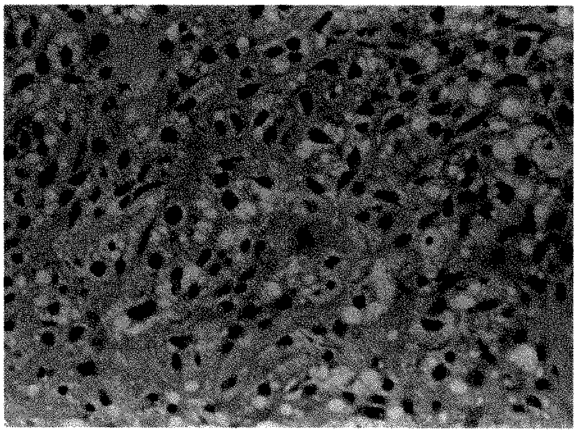

FIGURE 3. Malignant-appearing cartilaginous cells containing hyperchromatic pleomorphic nuclei (hematoxylin-eosin stain; magnification, × 160).

Discussion

Chondrosarcoma is the third most common malignancy of bone [1]. Tumors of lower histological grade grow slowly and remain locally invasive [1]. High-grade chondrosarcomas, do however, metastasize to organs such as kidney, spleen, jejunum and heart, and this spread takes place by intravascular growth and extension [1–4]. Primary intracranial chondrosarcoma constitutes only 0.16% of all intracranial tumors [5] and a metastatic lesion of the same category within the brain is even more rare. The presence of an enhancing lesion with or without calcification on CT scan in a patient with previously known chondrosarcoma supports the diagnosis of metastasis [5]. In this case, a diagnosis was confirmed by histological examination. Chondrosarcomas are resistant to radiotherapy and there is no known effective chemotherapeutic agent [6]. In appropriate situations, surgical removal remains the only treatment. The prognosis, as in other sarcomatous lesions, is poor.

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THIAMINE DEPENDENT ANEMIA IN DIDMOAD (WOLFRAM) SYNDROME: FURTHER STUDIES AND REPORT OF TWO ADDITIONAL CASES

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The DIDMOAD syndrome includes diabetes mellitus (DM) and optic atrophy (OA), variously associated with diabetes insipidus (DI), sensorineural deafness (D), dilatation of the urinary tract, and other minor abnormalities. Historically, the association of diabetes mellitus (DM) with optic atrophy (OA) was first described by Von Graeffe in 1858 as quoted by Fishman and Ehrlich [1]. Thereafter, in 1938, Wolfram [2] described a family of eight siblings, four of whom had DM and OA; three of the four affected siblings subsequently developed neurosensory hearing losses; and later, two developed neurogenic bladders. Since then, over 100 cases of this syndrome have been described in the literature and analysis of multiple pedigrees revealed an autosomal recessive mode of inheritance [1,2].

The akined but less common triad of thiamine responsive anemia, diabetes mellitus, and sensorineural deafness has been described so far in only 14 patients [3–12]. We describe two additional patients (sister and brother) both of whom presented with thiamine responsive anemia, diabetes mellitus, and sensorineural deafness.

Case Report

Case 1

A 5½-year-old Yemeni girl was initially seen in a primary care clinic at the age of two years because of unsatisfactory growth and pallor. Hematological tests at the time revealed that she was anemic and an iron therapeutic trial was exhibited but without benefit. During a follow-up visit at three years of age, her random blood glucose level was noted to be high at 14.8 mmol/L and she was then admitted for further work-up. During admission, insulin therapy was started after studies showed an elevated fasting blood glucose concentration (8.8 mmol/L) and an abnormal oral glucose tolerance test result. She was maintained on two daily doses of insulin, five units of NPH insulin plus two units of regular insulin in the morning and two units of NPH insulin in the evening. At five years of age, she developed bilateral sensorineural deafness confirmed by auditory evoked responses and audiometry. Her physical examination revealed a pale and deaf girl who was not in distress. Her weight was 15 kg (5th percentile) and her height 101 cm (< 5th percentile). There were several hyperpigmented cafe-au-lait-like spots on her trunk and extremities measuring 0.5 to 1 cm in diameter. Ophthalmic tests including electroretinography (ERG) and flash visual evoked potential (FVEP) revealed optic subatrophy mainly involving the right eye. The remainder of her physical examination was unremarkable.

Investigation of her anemia revealed a hemoglobin of 7.5 g/dl, hematocrit 21.8%, MCV 90.4 fl, MCH 31.2 pg, MCHC 34.5 g/dl, platelets 194 $\times 10^9$/L and leukocyte count 6.6 $\times 10^9$/L. The leukocyte differential was: neutrophils 23%, eosinophils 4%, monocytes 3%, and lymphocytes 70%. The peripheral blood smear showed severe anisopoikilocytosis with prominent macrocytosis. The neutrophils showed no hypersegmentation. The bone marrow was very cellular with an abundant megakaryocytosis but the erythropoietic cells

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showed megaloblastoid features and dyserythropoietic changes, increased stainable iron, and numerous ringed sideroblasts. The myeloid series showed normal maturation and differentiation. Serum iron was 9 mmol/L, iron binding capacity 32 mmol/L, ferritin 213 μg/L, vitamin B_{12} 423 pg/ml and serum and red cell folate were 4.3 and 3094 ng/ml, respectively.

The hemoglobin electrophoresis, G6PD level, liver function tests and serum electrolytes, urea and creatinine were normal. The direct and indirect Coomb's and Ham's test with sucrose were all negative. Because of the siderblastic changes in her bone marrow, she received a trial of pyridoxine for three months but without any benefit.

At the age of 4½ years, the patient was started on regular blood transfusions every four to six weeks because of inadequate growth and persistently low hemoglobin level in the range of 5 to 7 g/dl. She had received ten blood transfusions before a correct diagnosis could be made.

Case 2

The brother of Case 1, age 20–months, was seen with his sister when he was 4–months old. He subsequently developed left eye esotropia and deafness at the age of 6 and 13 months, respectively. Diabetes mellitus was discovered at 19 months of age when he was admitted for investigation of fever and a routine urinalysis showed glycosuria. At that time, his random blood sugar revealed a level of 14.3 mmol/L with no evidence of ketoacidosis. Subsequently, he had an oral glucose tolerance test which was normal. He was managed initially with regular insulin according to blood sugar level and eventually maintained on two units of NPH insulin once daily. His most recent physical examination revealed a pale looking child with left convergent squint and profound deafness. His weight was 9.8 kg (5th percentile) and his height 81 cm (25th percentile). There was no organomegaly, abnormal skin lesions or other remarkable findings.

Laboratory investigation revealed a hemoglobin of 5.9 g/dl, hematocrit of 16.7%, RBC 1.99 × 10^{12}/L, MCV 84.1 ft, MCH 29.6 pg, MCHC 35.3 g/dl, and platelets 279 × 10^{9}/L with a differential count of 37% neutrophils, 54% lymphocytes, 8% monocytes, and 1% eosinophil. The reticulocyte counts was 0.6%. The serum iron, iron binding capacity, ferritin, folate and vitamin B_{12} were within normal limits. Haptoglobin, total bilirubin and hemoglobin electrophoresis were also within normal limits. The peripheral blood smear and bone marrow findings were similar to those of his sister, but with a decreased number of ringed sideroblasts and slight increase in stainable iron in the bone marrow. The audiologic and ophthalmic tests revealed severe bilateral sensorineural deafness and infantile esotropia involving the left eye. His HbAIC was 10.8%.

In both siblings, electrocardiogram, electroencephalogram and intravenous pyelography were normal. Also, investigations for organic aciduria and diabetes insipidus were negative. The two siblings are the only children of a first cousin couple with no family history of anemia, deafness, or diabetes.

The blood transketolase activities and thiamine levels were determined by Bioscientia in Germany in the two siblings and their parents using the HPLC method described by Wielders and Mink [13] (Table 1).

Administration of thiamine, 100 mg, daily administered orally resulted in prompt increase in the hemoglobin levels of both children within two weeks. In Case 1, the Hb was 6.1 g/dl pretreatment, and increased to 10.1 g/dl at the end of the second week, while in Case 2, the Hb was 5.9 g/dl pretreatment and 11.3 g/dl at the end of the second week of treatment. Reticulocytes revealed peaks of 80,000 and 90,000/mm^2 respectively in the two children at the end of the first week, but the mean corpuscular volume was unchanged in both cases.

The insulin requirements decreased in both siblings to approximately one-half of their initial doses. The plasma C-peptide level increased during therapy in both children especially in the girl (Table 1).

Discussion

The DIDMOAD syndrome in its original form, as reported by Wolfram [2] described the association of diabetes mellitus and optic atrophy but with no mention of diabetes insipidus and deafness. It is now known that sensorineural deafness or abnormal audiometry occurs in at least 39% of

TABLE 1. *Blood thiamine, transketolase and C-peptide level in the two patients and their parents.*

	Case 1	Case 2	Father	Mother
Blood thiamine level (16–48) ng/ml				
before treatment	52 ng/ml	66 ng/ml	44 ng/ml	21 ng/ml
during treatment	50 ng/ml	60 ng/ml		
Blood transketolase (0.75–1.30) IU/gHb				
before treatment	1.24 IU/gHb	1.19 IU/gHb	0.89 IU/gHb	1.08 IU/gHb
during treatment	1.29 IU/gHb	1.3 IU/gHb		
* C-peptide level (0.1–1.8) nmol/L				
before treatment	0.22 nmol/L (11.1)	0.18 nmol/L (12.9)		
during treatment	0.28 nmol/L (8.9)	0.56 nmol/L (6.7)		

* With concomitant fasting blood glucose level in parenthesis mmol/L.

cases, central diabetes insipidus in 32% and dilatation of the lower urinary tract in 19%, with many other additional abnormalities occurring in smaller portions of patients [2]. A less frequently encountered triad of thiamine-responsive sideroblastic anemia, diabetes mellitus and sensorineural deafness was first recognized by Roger et al [3] in 1969, but Borgna-Pignatti et al [12] has recently suggested that the triad could be part of the wider spectrum of DIDMOAD syndrome, with both conditions resulting from a defect of thiamine metabolism.

In our patients, the peripheral blood and bone marrow findings strikingly corresponded to thiamine-responsive anemia described in association with diabetes mellitus and sensorineural deafness [3–12]. A good response to therapy with thiamine, and in particular, the significant increase of hemoglobin level with brisk reticulocytosis confirms this diagnosis. Also, the increase in plasma C-peptide concentration which paralleled the reduction in insulin requirement suggests an increase in endogenous insulin production. This fact together with absence of an HLA-DR_3 or DR_4 haplotype in most of the reported cases suggests that the cause of diabetes in this syndrome may differ from the more common type of insulin-dependent diabetes mellitus and is most probably linked with thiamine metabolism [1,12].

To date, blood thiamine levels and the activities of thiamine-dependent enzymes have been studied in only seven of the fourteen patients affected by this syndrome. However, the results of the studies have not been conclusive and there are some conflicting results. Our patients, as well as their parents, had normal thiamine levels and blood transketolase activities which are in agreement with the findings in the original patient described by Rogers et al [3] who had a normal thiamine level as well as normal pyruvate dehy-drogenase, ketoglutarate dehydrogenase and transketolase activities. These enzymes use thiamine as a cofactor in carbohydrate metabolism. Blood transketolase activity was normal in the patients reported by Mandel et al [6] and by Rosskamp [11]. In contrast however, Borgna-Pignatti et al [12] and Poggi et al [9] found a reduced level of thiamine as well as of thiamine pyrophosphokinase, an enzyme that phosphorylates thiamine to its metabolically active form, thiamine pyrophosphate. Also, Abboud et al [8] found the activity of alpha ketoglutarate dehy-drogenase to be very low in leukocytes, but not in fibroblasts. The exact thiamine-related biochemical abnormalities in thiamine-dependent anemia therefore remains to be more definitely delineated, but a thiamine dependency state is not in doubt, at least as far as the anemia is concerned. In this regard, the disorder is similar to other recognized vitamin dependencies or vitamin responsive inborn errors of metabolism [14–16]. Whether a thiamine dependency state underlines the various clinical manifestations present in the DIDMOAD syndrome remains speculative at the present time [12], and further studies to define the exact metabolic relationships are needed.

Acknowledgments

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SQUAMOUS PAPILLOMA OF THE ESOPHAGUS: A CASE REPORT AND REVIEW OF THE LITERATURE

Rashed S. Al-Rashed, FRCP(C)

Squamous papilloma of the esophagus is a rare benign tumor [1] which is defined as a "sessile lesion with central core of fibrovascular tissue, capped by squamous epithelium" [2]. In 1959, Adler et al [3] reported the first well-documented case of squamous papilloma diagnosed by thoracotomy. Several reports of this rare benign tumor reached the literature with endoscopy being the main diagnostic procedure [4]. There is no report of this lesion from the Middle East in the literature.

Case Report

A 37-year-old Yemeni man presented with dysphagia of two months duration for solids, weight loss of 1 kg over the last month and epigastric pain for the last six months. He denied food regurgitation, water brush, hematemesis or melena. He does not smoke or drink alcohol and did not use aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAID). He had a history of duodenal ulcer 12 years ago which was medically treated and over the past 12 years has had on and off epigastric pain. Review of systems, family history and social history were uncontributory. Physical examination revealed a well-built man in no distress with a temperature of 37°C, pulse 88/min and regular, good volume and blood pressure of 120/80 supine. Physical examination revealed no abnormalities. A full blood count, chest x-ray and stool analysis were normal. He had a positive HBsAg. Esophagogastroduodenoscopy showed a polypoid lesion measuring 10 mm in diameter in the distal esophagus just above the gastroesophageal junction which was sessile, pink in color, and soft with a smooth, slightly rough surface (Figure 1). There was patchy hyperemia in the antrum with normal first and second parts of the duodenum. Biopsies of the lesions showed squa-mous cell papilloma with no evidence of malignancy. The patient was re-endoscoped and a polypectomy was performed with no complications. The histology of the polyp showed squamous cell papilloma with a fibrovascular core covered by stratified squamous epithelium (Figures 2a and 2b). The patient was followed up for one year with no recurrence of his symptoms. Follow-up endoscopy was scheduled but the patient did not return for endoscopy.

Discussion

Squamous papilloma is a rare benign tumor of the esophagus. Autopsy reports by Moersch and Harrington [5], Plachta [6] and Attah and Hajdu [7] estimated an incidence of 0.04%, 0.01%, and 0.006%, respectively. With the wide use of flexible fiberoptic endoscopy, the incidence has increased, 0.04% [8], and 0.075% [9]. In contrast to the literature, Sablick et al [10] found a 0.45% prevalence. This high prevalence was attributed to the increased proportion of esophageal disease, mainly cancer of the esophagus registered in their region compared with other regions in Italy. In 6,084 endoscopies performed in our unit only one case of squamous papilloma was found; thus the incidence is 0.016%, which is similar to the reported literature.

Our patient, a 37-year-old male, is younger than the reports of the fifth decade being the average age [4]. The lesion was a single polyp 10 mm in size and located in the distal esophagus which is

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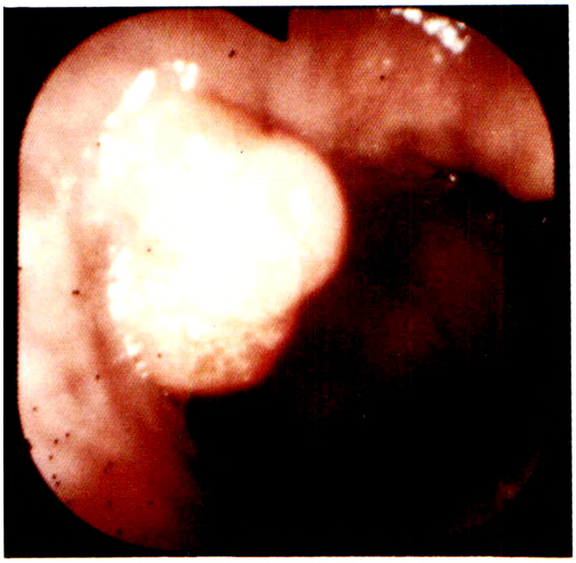

FIGURE 1. Squamous papilloma of the esophagus.

the most common presentation [8-12]. The symptoms in squamous papilloma are complex [4], variable [13] and non-characteristic [14] with epigastric pain being most common [4].

The etiology of squamous papilloma is unknown [14]. Viral infection [15], chronic irritation by trauma or reflux [1,16] and potential chemical induction which was demonstrated in rats [17], all have been postulated. All these causes have not been proven and no intercellular inclusion bodies or viral particles have been found [11,18]. There is a wide discrepancy between the number of patients with reflux and the number of papilloma [12] and there is no animal model for esophageal papilloma [16].

Squamous papilloma of the larynx [19,20] and cervix [21,22] are thought to be precursors to squamous cell carcinoma. However, in the esophagus, they appear benign histologically and have never been reported to be invasive [14], but long-term follow-up of a large number of cases has not been done. Distinguishing benign from malignant process should be made after microscopic examination of the completely resected tumor [1]. Endoscopic removal and follow-up should be performed as has been suggested by other reports [11,14,16].

In conclusion, although squamous papilloma of the esophagus is rare, endoscopists should be aware of it since endoscopic removal is a feasible therapeutic approach.

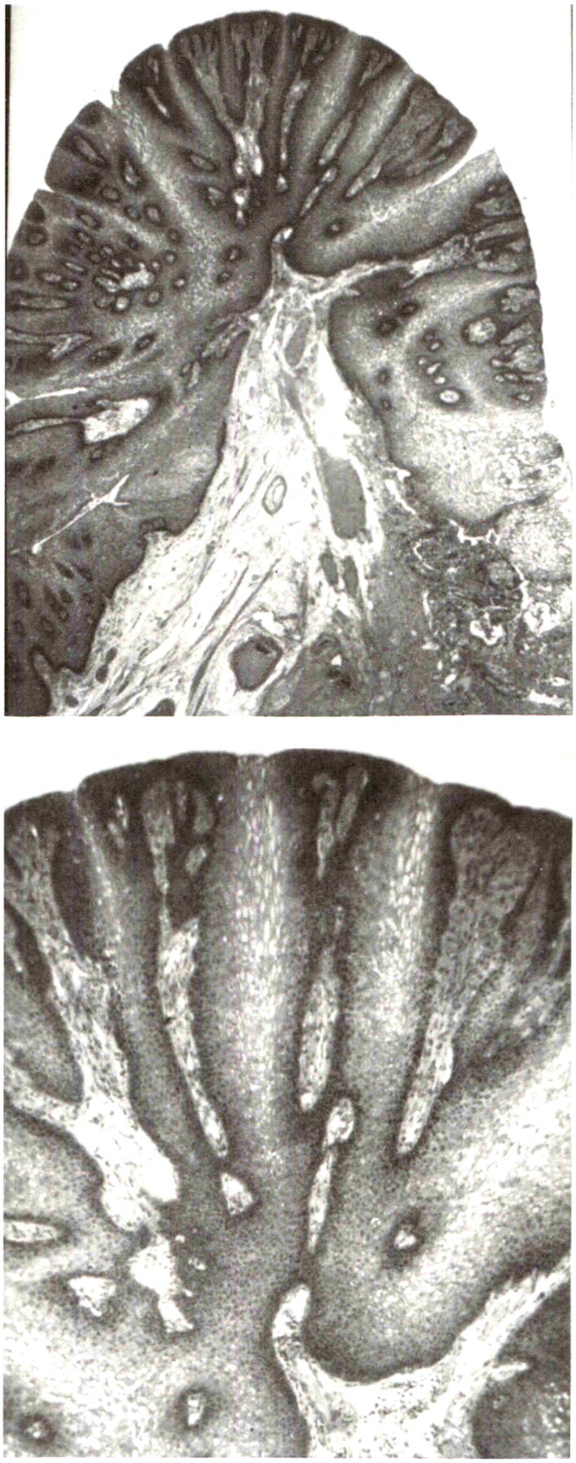

FIGURE 2. (A) Low power view of squamous cell papilloma showing average vascularity of the connective tissue core with squamous epithelium layers (hematoxylin-eosin stain; magnification, × 20). (B) segment of squamous cell papilloma (hematoxylin-eosin stain; magnification, × 100).

Acknowledgments

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HYDATIDOSIS MIMICKING METASTASES

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In three cases hydatid cysts were initially misdiagnosed as metastases. A case of biopsy-confirmed hypernephroma showed multiple bilateral rounded densities in the lungs suggesting metastatic disease. A second case with cystic expansive lesion of the liver clinically diagnosed as "cystic hepatocellular carcinoma" was combined with multiple bilateral "nodules" of the lungs mimicking metastases. A third case with biopsy-confirmed hypernephroma demonstrated multiple hepatic lesions thought to be metastases. Computed tomography (CT) was helpful in disclosing these low density lesions as hydatidoses.

The recognition of a malignant tumor coexistent with hydatid disease is important for appropriate and effective treatment both of the malignant tumor and the parasitic infection. Today, powerful benzimidazole compounds make successful chemotherapy treatment feasible even in widespread or disseminated hydatid disease. Recognition of these lesions is, therefore, crucial for potential cure.

Ultrasonography (US) computed tomography (CT), and magnetic resonance imaging (MRI) have, to a large extent, replaced less effective and invasive methods. Alone or in combination with each other, they are helpful in assessing uni- or multilocular lesions throughout the body, including the lungs [1–5]. Hydatidosis and tumor may look very similar [6,7]. In cases where extrapulmonary malignant tumor has been confirmed by biopsy, the occurrence of multiple rounded densities in the lungs are usually interpreted as metastases. Even without a known primary tumor, multiple hydatid cysts in other organs or tissues may closely resemble neoplastic deposits and be confused with metastases. Their recognition is, therefore, extremely important for appropriate therapeutic management as a precondition for cure [8].

Case Reports

Case 1

In a 51-year-old man, a space-occupying lesion of the left kidney was discovered. A CT of the abdomen and kidneys (Figure 1a) confirmed the presence of a 13 cm in diameter large mass of the left kidney with irregular density and a tiny area of calcification. No evidence of lymphadenopathy or extrarenal extension was found. A fine needle aspiration biopsy revealed a renal cell carcinoma. On the preoperative chest radiography, two rounded bilateral densities in the lower lobes were seen (right 2.5 cm and left 6 cm in diameter) thought to be metastases. It was therefore assumed that the patient was inoperable. CT of the chest, however, showed that the lesions were cystic. Since the density was between 10 and 20 HU, infected cysts or hydatid disease (Figure 1b) could not be excluded. Serological examinations revealed very high echinococcal titers (IHA 1:2, 048; normal values up to 1:32) confirming the presence of hydatid disease. A radical left nephrectomy was, therefore, still possible and carried out before renal metastases had developed.

Case 2

A 46-year-old man suffered from shortness of breath for three years, weight loss and cough. In the past, he had coughed up a small amount of blood. The chest radiographs showed multiple bilateral "nodules" (Figure 2a) (arrows) from .5 cm to several centimeters in diameter thought to be metastases. Ultrasonography of the abdo-

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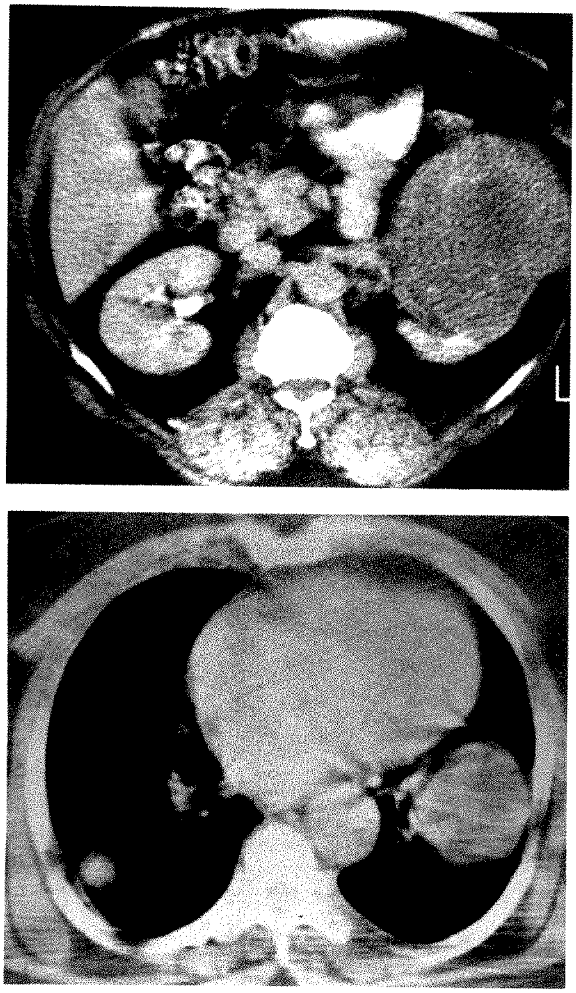

FIGURE 1. 51-year-old man with left kidney mass; (a) contrast enhanced CT; (b) non-enhanced CT of the chest.

men showed a large mass with cystic areas in the right lobe of the liver. CT of the liver confirmed the cystic nature of the mass, first falsely assumed to be a cystic hepatocellular carcinoma (Figure 2b). CT of the chest showed multiple bilateral "nodular" lesions on parenchymal window setting. On soft tissue window settings, some of these lesions were air-filled and/or demonstrated "folding membranes" (Figure 2c), strongly suggesting the diagnosis of echinococcosis (arrows). Serologic tests (Indirect Hem Agglutinin - IHA) were performed and titers were found to be highly elevated (1:4096) confirming the presence of hydatid disease.

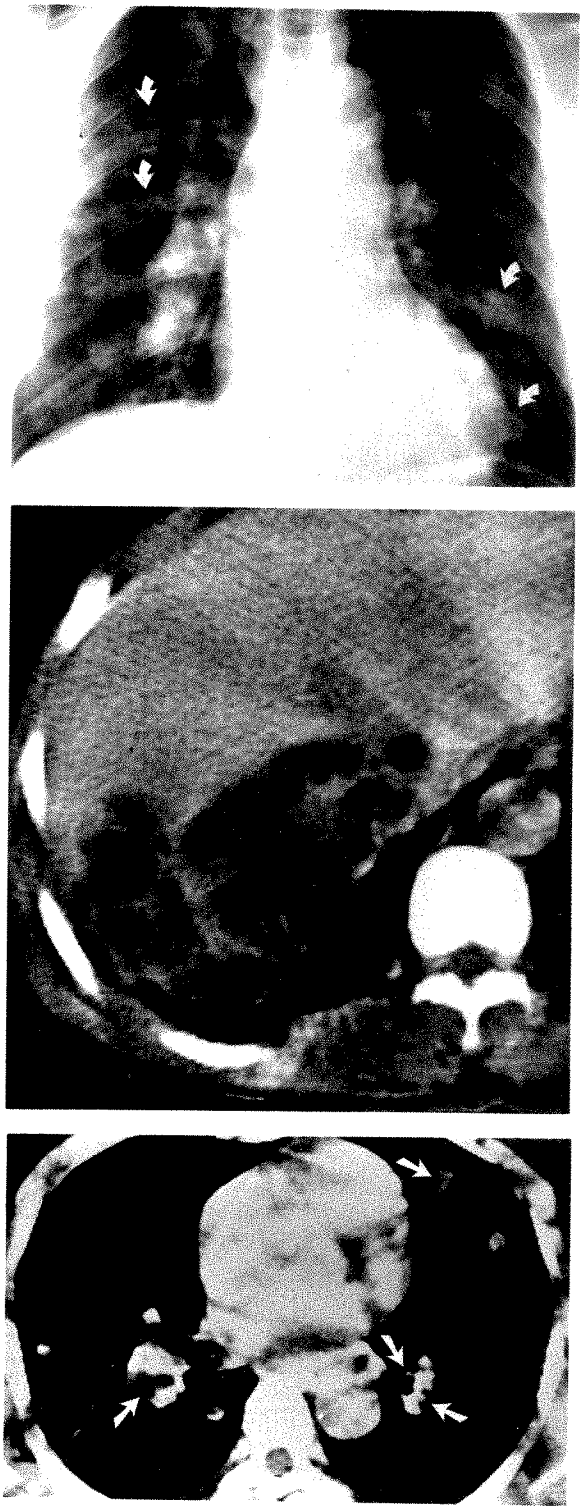

FIGURE 2. 46-year-old man with bilateral nodules suggestive of metastases with expansive lesion of the liver, thought to be a "cystic hepatocellular carcinoma"; (a) chest radiograph, PA; (b) non-enhanced CT liver; (c) non-enhanced CT of chest.

Case 3

A 51-year-old woman suffering from hypertension was admitted with abdominal pain and angina pectoris. On physical exam, the liver was found to be enlarged. Abdominal radiographs showed calcifications in the liver. Ultrasonographically hypoechoic lesions of the left liver lobe and of the right kidney were seen. Non-enhanced and enhanced CT showed: (1) a 16 cm in diameter, large space-occupying lesion of the right kidney, presumably a cystic hypernephroma without invasion of the inferior vena cava (Figure 3a), (2) two other space-occupying lesions first thought to be cystic metastases, one in the left lobe of the liver (6 cm in diameter) and the cystic duct area (4 cm in diameter) with liver calcification. An abdominal angiogram (Figure 3b) and a selective renal arteriogram was, therefore, performed which confirmed a hypovascular mass in the right kidney. On the basis of these examinations, a presumptive diagnosis of a right hypernephroma was made. During surgery, a right radical nephrectomy and hydatid cystectomy with drainage of the hydatid cyst which had ruptured into the left hepatic duct, was performed.

A T-tube cholangiogram demonstrated the presence of communication between the cystic duct and the hydatid cyst. Microscopy confirmed the presence of scolices (Figure 3c) and daughter cysts.

Pathology of the surgical specimen showed: (1) renal cell carcinoma of the right kidney; (2) hydatid cyst of the liver; (3) hydatid cyst of the cystic duct.

Discussion

If a confirmed hypernephroma presents with bilateral pulmonary rounded densities, metastases are usually assumed to be present. In areas where echinococcosis is endemic, the presence of hydatid disease has always to be suspected and excluded [13,14]. A variety of lung lesions may have a similar appearance to hydatid cysts (e.g., primary tumors, metastases, cysts, inflammatory lesions, abscesses). Recognition of coexisting pulmonary echinococcosis in a cancer patient is extremely important since the disease may otherwise be regarded as inoperable and/or incurable, and the patient, therefore, may not get the benefit of a curative treatment. With cancer treatment alone, the coexisting parasitic disease is left

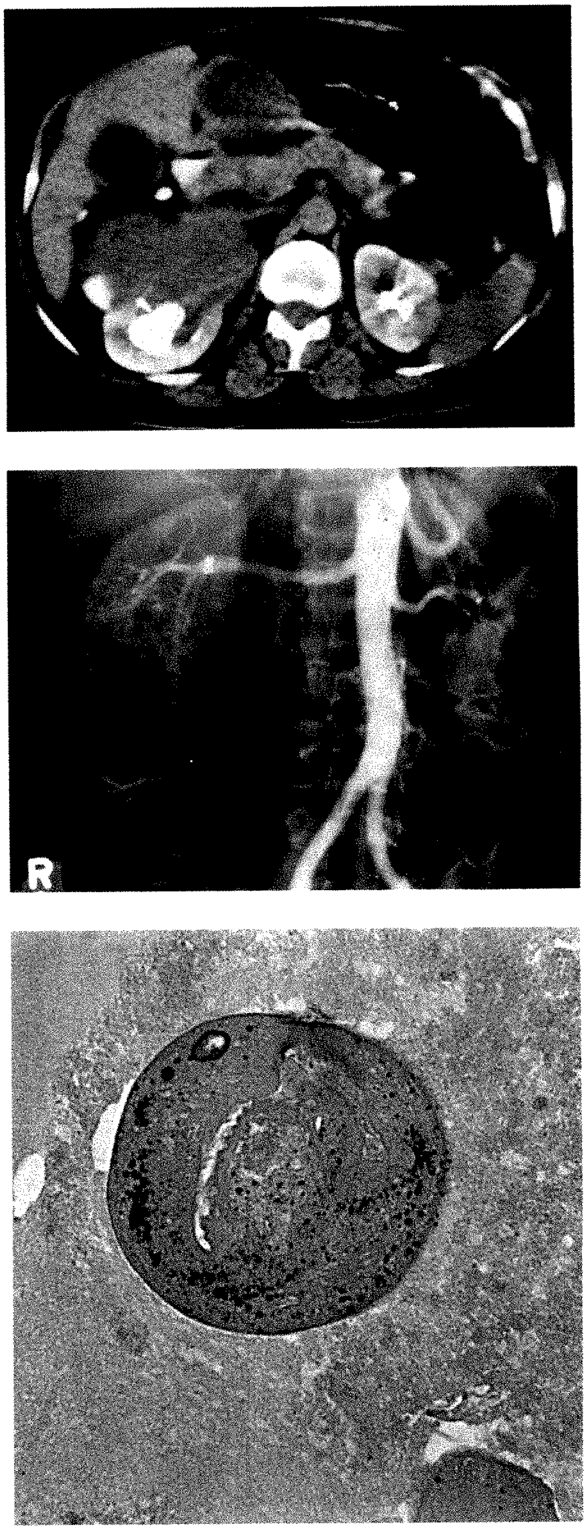

FIGURE 3. 51-year-old woman with right-sided renal mass and multiple hepatic lesions assumed to represent metastases; (a) CT, kidneys and liver; (b) aortogram; (c) Scolex in hytatid cyst.

untreated and may progress and lead to invalidity or kill the patient, even when the cancer is cured.

Recognition of hydatid disease may be difficult, especially if it is not included in the differential diagnosis. Serologic tests in echinococcosis of the lungs may be helpful. However, false negatives occur and may, at times, confuse diagnostic conclusions and therapeutic management.

Ultrasonography allows differentiation of solid tumors from cysts [10]. It is especially helpful in abdominal hydatid cysts [10] specifically if a "double-line" sign is present (Figure 4), demonstrating parasitic membranes of a hydatid cyst [1,2,5] and if brood capsules or daughter cysts are demonstrated. However, ultrasonography is of limited value in lung echinococcosis unless an acoustic window is available, such as occurs if the cyst is located in the vicinity of the thoracic wall or contiguous to an effusion.

Magnetic Resonance Imaging (MRI) has the disadvantage of relatively long acquisition time causing motion blur and artifacts. There is less resolution than on CT. Calcifications are less well seen than on CT due to signal drop out. Small calcifications may, therefore, be easily missed. MR imaging findings of hydatid disease in the liver, chest [1-3,5,11] have been reported. However, the presence of characteristic or diagnostic findings such as a low signal intensity rim on T2 weighted images representing the cyst wall, cyst rupture and "folded parasitic membranes" called "serpent sign" [1-3,5] has only most recently been described. If present, it may allow a confident diagnosis of hydatid disease in some cases even if serologic tests should be falsely negative [1-3].

These signs have also been observed in hydatid cysts in other locations such as liver, spleen, brain [12], and other organs. Moreover, the result of an appropriate chemotherapy of widespread or disseminated hydatid disease can directly be followed by sequential MRI which also has the advantage of being non-invasive and having multiplanar imaging facilities without the risk of ionizing irradiation.

Computed Tomography (CT) in echinococcosis of the lung offers additional information [6] to other modalities. It has the advantage of higher resolution and recognizes even tiny calcifications. In our cases, CT provided additional clues for coexistent hydatid cysts in the lungs and liver leading to a confirmed diagnosis. In case one, CT showed two rounded lesions averaging 10 to 20 HU, compatible with cysts containing some protein, such as may occur with hydatid cysts.

In case two, the chest radiograph showed multiple bilateral nodules of varying size suggesting the presence of pulmonary metastases. CT visualized inhomogeneity of structures where demonstrated collapsed parasitic membranes allowed the diagnosis of hydatid disease. In case three, low density expansive lesions in the liver, first thought to be metastases of a verified hypernephroma, were identified by CT as cystic and confirmed by pathology as hydatid cysts.

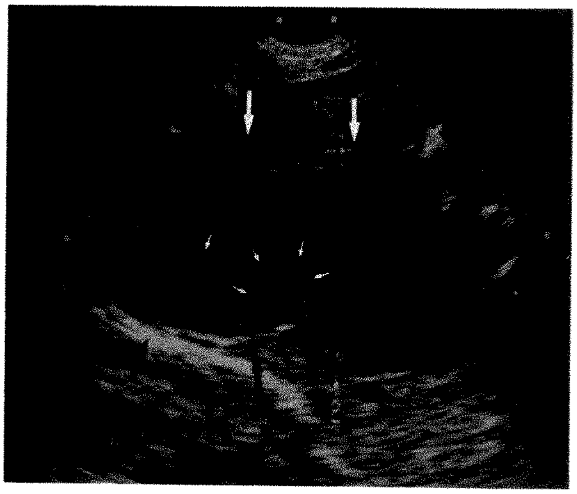

FIGURE 4. Hydatid cyst of the liver (ultrasonography) showing characteristic "double line" (large white and black arrows) due to loose parasitic membranes and rounded structure compatible with brood capsule (small white arrows).

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Meningitis in Children in Elmadina ElMunowara

To the Editor: I read with interest the report on meningitis in children by El-Amin et al [1]. The main outcome in this study was to demonstrate that overall mortality and morbidity is comparatively low in Saudi Arabia.

In our study of bacterial meningitis in children in Asir (which is in the southern region), 79 children (post-neonatal period) were diagnosed over a three year period. The overall mortality and morbidity in our series was 6.3% and 37.9%, respectively when compared with other regions of the Kingdom (Tabuk [2] which is in the north, and Dammam and Al-Khobar [3] which are in the eastern part of the Kingdom) (Table 1).

TABLE 1. *Mortality and morbidity in meningitis in children in various regions of Saudi Arabia.*

Region, Author, Year	Cases	Mortality (%)	Morbidity (%)
East (Dammam, Al-Khobar) Abomelha et al, 1988	161	14.4	Not recorded
North (Tabuk) Azubuike, 1990	49	14.3	38.8
West (Elmadina Elmunawara) El-Amin et al, 1991	122	3.27	17.2
South (Asir) Nabi et al, 1990	79	6.3	37.9

Etiological organisms identified from cerebrospinal fluid (CSF) of these patients in all the four studies are the same (i.e., *Neisseria meningitidis, Hemophilus influenzae, streptococcus pneumoniae),* in their study [1]. Viral and tubercular meningitis cases are also included.

In our study, 53% of children were less than one year of age compared with 41.3% in the above study [1]. This may also partly explain the slightly higher mortality rate observed in our series.

In view of the better outcome of the Elmadina Elmunowara study [1], I would be interested to know the drug regime used for treating these patients and percentage of drug resistance in their experience.

Drug resistance observed while treating these cases in other regions were in our study in the Asir region 11.7% ampicillin and chloramphenicol, in Tabuk 11% to ampicillin and 7% to ampicillin and chloramphenicol, and in the eastern region 14% to ampicillin.

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Reply

To the Editor: I thank the author for his interest in our article. In our study *H. influenzae* was 100% sensitive to chloramphenicol with 48% resistance to ampicillin. *N. meningitidis* was 100% sensitive to penicillin with ampicillin resistance of 9%. Pending culture results we started treatment of infants below three months of age with penicillin and amikacin and older children with penicillin and chloramphenicol. We also gave prophylactic phenobarbitone and dexamethasone routinely after confirming the diagnosis of meningitis.

We are reminded about meningitis each "Haj" and hence we have a high index of suspicion for it. In addition, we have a low mortality because we deal with more cases of meningococcal disease which has a better prognosis than others.

We only reported about the short-term hospital morbidity in our study and we need to look into the long-term one, particularly the sensorineural deafness.

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Scorpion Envenomation in Marjadah Children

To the Editor: We read with interest Neale's review [1] of the scorpion sting syndrome in eastern Riyadh. One of the 205 cases seen over a five-year period, 29 [14.1%) were children of whom only two were hospitalized. No deaths were recorded in the entire series.

As a comparison, we present our experience in a retrospective review of scorpion envenomation in children over a two-year period (June 1988 to May 1990) at the General Hospital Majarda which is located in the hot mountainous Asir Region of the Kingdom.

Over this period, 400 patients with scorpion stings went through the emergency room (ER) of the hospital. Of this number, 188 (47%) were children aged 12 years or younger. One hundred fifty-six of these (7.5% of the total pediatric admissions) were hospitalized, whereas relatives of 32 children refused to give consent for admission.

There were 83 boys as opposed to 73 girls. Fifty-seven (36.5%) were four years of age or younger, 54 (34.6%) older than four to eight years and 45 (28.8%) older than eight to 12 years. Similar to Neale's findings in Riyadh, less envenomations occurred during the daytime [1]. Seventy percent of the stings were during the night and early hours of the morning as opposed to 30% during the daytime. There were also seasonal variations with only 26 cases (16.7%) presenting during the three winter months (November, December and January).

Common clinical signs and symptoms as documented in the case records were namely: varied degrees of pain 140 (89.7%), erythema and minimal swelling 53 (34.0%), relative hypertension with tachycardia 42 (26.9%), tachycardia alone 30 (19.9%); frothing, hypersalivation and vomiting 37 (23.7%) and cold extremities (19.9%). These features were in some cases associated with more serious cardio- and neurotoxic symptoms. On the whole, 19 (12%) children (of whom 11 were four years or younger) presented with such systemic complications that necessitated closer observation and care in the hospital for more than three days (Table 1).

Except for the very toxic sorpion *Leiurus quinquestriatus* which we were able to identify at the very late stage of the study a systematic attempt at identification of the various scorpions was not made in this retrospective study. However, from the list of scorpions found in Saudi Arabia [2], it is evident that other toxic varieties found in the Al-Baha Region where mortality rate for scorpion stings is about 2.3% [3], also exists in the Asir Region. These include the *Androctonus cras-*

TABLE 1. *Major systemic findings in 19 children with hospital stay greater than 3 days.*

	0–2	>2–4	>4–6	>6–8	>8–10	>10–12	Total
Delirium and cardiogenic shock	2	2	1		1	1	7
Delirium and sinus tachycardia	1	1	1				3
Sinus tachycardia and congestive heart failure	1	1					2
Cardiogenic shock		1		1			2
Gross abdominal distention and delirium			1	1			2
Convulsions and delirium		1					1
Dehydration and irritability	1						1
Urinary retention				1			1
Total	5	6	3	3	1	1	19

sicauda and *Compsobuthus werneri*. In regard to therapy, all the patients in our series routinely received antiscorpion venom in the ER (if not already given at the primary health center [PHC]). They were usually placed on a slow maintenance infusion of 5% dextroxe in water and less frequently with mixtures of saline where indicated. Other supportive measures included tetanus toxoid, an antihistamine or antiemetic and topical 2% xylocaine injection or ice pack. Children who were very agitated, irritable and delirious received chlorpromazine (largactil) 0.5 to 1.0 mg per kg intramuscularly (IM) one or more times. If there was associated hypotension or cardiogenic shock, largactil was given only after the blood pressure had been brought up to a satisfactory level. Intravenous diazepam (valium) was occasionally used to treat children with gross irritability or seizures if the blood pressure was stable. Bolus doses of phenobarbitone were not given because of the possibility of respiratory depression or arrest. According to Rimsza et al [4], its use has neither decreased morbidity nor mortality.

Seven of the nine patients with cardiogenic shock were placed on dopamine infusion (10 to 15 mcg/kg/min) and the dose tapered off gradually over 24 to 48 hours. In addition, hydrocortisone was given simultaneously. Two children in cardiac failure received digoxin. Although the effectiveness of the scorpion antivenom has been in doubt [5] unlike in Neale's review [1], this was given routinely to our patients. No side effects and no specific advantages could with certainty retrospectively be traced to the use of the antivenom. In both reviews mortality was nil.

On face value, it might appear that many of the children in our series did not require hospitalization. However, in view of the rural location of our hospital and the insufficient facilities for observation in the ER, we chose to be cautious and liberal in our admission policy toward children with scorpion envenomation. From our observation, it is not unusual to find young children who develop hypotension or cardiogenic shock after appearing initially stable. According to Balozet [6], symptoms of envenomation may last as long as 24 hours and on the average four hours. The concept that the scorpion sting is not generally fatal to healthy adults in Africa and the Middle East [7] is definitely not applicable to children. Infants and children under the age of four years are very susceptible to scorpion envenomations [8]. Thus, it appears indicated that children in this age group should preferably be admitted and observed more closely before discharge. Such precautionary measures may help avoid the rather high mortality rate of about 25% to 50% in children in the Middle East which has been reported by Khan [9].

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Morphological and Immunological Pattern of Blastic Transformation in Chronic Myeloid Leukemia

To the Editor: I read with interest the recent article published by Roberts et al [1], regarding the morphological and immunological pattern of blastic transformation in chronic myeloid leukemia (CML) in Saudi Arabia. What really attracted my attention was the ten years age difference between the Saudi and Western patients. Their mean age of 38.2 years is at least a decade younger than most of the world figures. It has been suggested by the authors that this disparity is due to the younger age group of the Saudi people. I think I have a more reasonable explanation for this significant age group difference in a disease which is generally well known to have a characteristic pattern of evolution, course and age group.

King Faisal Specialist Hospital and Research Centre (KFSH&RC) is the only referral center of its kind in the Kingdom and the Middle East. With a bone marrow transplantation (BMT) program, which so far has performed 255 allogeneic operations [Andrew Padmos, MD, personal communication], it is certainly one of the forerunners in the developing world. However, there are many other similar sized tertiary care hospitals in the Kingdom (my center included), which only refer CML patients to KFSH&RC if and when BMT is contemplated, that certainly means selective patients who are younger than 40 years of age. It is now well established that more than 60% of young CML patients can be cured of their disease if transplanted early in the chronic phase [2]. In the middle age group (the main bulk of these patients), transplantation is less rewarding and chemotherapy remains the cornerstone of their symptomatic management.

I would like to emphasize that quite a substantial proportion of CML patients in the KFSH&RC are referred from other centers for consideration of BMT. The main bulk of patients are managed locally. To support my assumption, refer to Table 1. It reports the number, mean and median age of patients who are under my care in a referral hospital that has cared for a nearly one million population in the Asir region of Saudi Arabia, over the last one thousand days (since the opening of our new Asir Central Hospital). Out of 27 patients, only five were referred to the KFSH&RC, those were all for consideration of BMT. The rest of the patients were managed in our hospital. It is clear that our mean age of 50.6 years correlates much better with the Western figures than with the Saudi figures proposed by the authors. Those five patients who were transferred to KFSH&RC were 16, 29, 30, 30, and 38 years of age, respectively. I am sure that there are many other similar hospitals in the Kingdom which only refer their young patients to the KFSH&RC. Perhaps diluting the authors' patients with ours will yield a similar age group as in the Western series.

TABLE 1. *Age patterns of 27 patients with chronic myeloid leukemia from Asir Central Hospital of Abha over a one thousand day period.*

Variables	Males	Females	Total
Number	16	11	27
Mean age + SD (yr)	52.9 ± 21.9	47.2 ± 19.5	50.6 ± 20.8
Median age (yr)	50	42	50

In conclusion, I assume that CML maintains its reputable uniformity in course, pattern of evolution and age group. Perhaps the younger age group of the KFSH&RC patients is because they are only getting the tip of the iceberg while we remain managing the majority of these patients.

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1. Roberts G, Padmos A, Clink H, et al. Morphological and immunological pattern of blastic transformation in chronic myeloid leukemia in Saudi Arabia: study of 90 transformations among 248 patients. Ann Saudi Med 1991;11(3):271-5.
2. Goldman J, Apperley J. Bone marrow transplantation for chronic myeloid leukemia. Progress in bone marrow transplantation, volume 53. New York: Alan R. Liss, Inc., 1987;97-102.

Reply

To the Editor: I thank Dr. Sheikha for his comments on our paper which described the morphological and immunophenotypic patterns of blastic transformation in Saudi patients with chronic myeloid leukemia CML [1]. He points out that the relatively young age of our patients contrasts with his own observations at the Asir Central Hospital in Abha. There, the mean and median ages of 27 patients he saw over a three year period was approximately 50 years, more

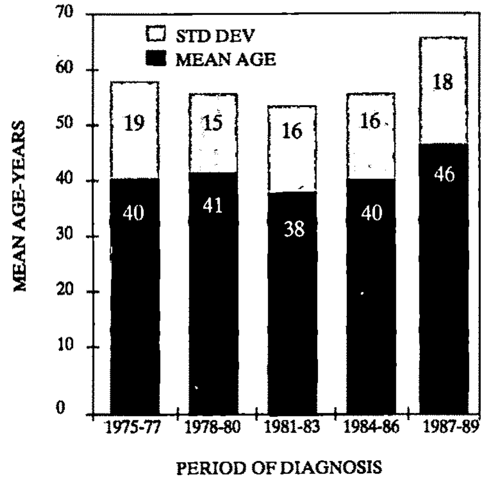

FIGURE 1. Shows the mean ages (± SD) at diagnosis of CML patients at the King Faisal Specialist Hospital and Research Center between 1975 and 1989.

consonant with world figures. He suggests that our lower age reflects referral patterns to the King Faisal Specialist Hospital and Research Centre (KFSH&RC) because of protocol requirements of bone marrow transplantation (BMT). Patients of less than 40 years are usually selected for this procedure, influencing the referring hospitals on whom to refer.

I do not think that this interpretation is likely to be correct because analysis of age patterns of our patients show no significant difference between years of presentation and diagnosis, either by individual years or by triennia (Figure 1). Since BMT for CML commenced at the KFSH&RC in 1984, a fall in the age should have become evident in that year, or at least in subsequent ones. This is not the case. Instead, the mean age has remained constant at around the 40 year level, except that in the last triennia to 1989, the level increased to 46 years.

It is probably premature to exaggerate the significance of this trend, but it would be interesting to see if it is maintained over the next few years.

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1. Roberts GT, Padmos MA, Clink H, et al. Morphological and immunological pattern of blastic transformation in chronic myeloid leukemia in Saudi Arabia: study of 90 transformations among 248 patients. Ann Saudi Med 1991;11(3):271-5.

Speciation and Biotyping of Brucella

To the Editor: With reference to a recent letter to the editor by Eltigani et al [1], we concur that speciation and biotyping of *Brucella* provides an excellent tool in understanding the epidemiology of brucellosis. However, their contention that "no significant work has been done to identify the species and biotypes responsible. The only published work was that of Corbel..." is not completely justified. Several investigators have reported their findings on the incidence of *Brucella* species and biotypes both in man and animals. Our cursory survey of literature, which we feel is far from complete, showed that of 527 cases of brucella cultured from humans in the last eight years, 517 (98%) were identified as *B. melitensis* and the rest as *B. abortus* [1–7]. Madkour [8] reported a moderate distribution of *B. melitensis* and *B. abortus* in animals and an understandable absence of *B. suis*.

Although Corbel [9] has found all three biotypes of *B. melitensis,* Qadri et al [2] reported that 64% of their 153 *B. melitensis* isolates from a major tertiary care center in Riyadh were biotype 1 and the rest biotype 3. Recently, Bilal et al [3] found that all the 70 isolates from the Asir region were biotype 3. Distribution of biotypes of *B. melitensis,* including those reported by Eltigani et al [1], is shown in Table 1.

Since biotype 1 is more common in African countries, its high prevalence in Saudi Arabia may be due to the import of animals from these countries for slaughter as well as breeding purposes. Biotype 3 is usually associated with nomadic herds and its second highest incidence reflects the nomadic heritage in the Kingdom.

Although several reports from the Central region of the Kingdom have dealt with speciation and biotyping, there are gaps in their prevalence from other parts of the Kingdom. We agree with Eltigani et al [1] on the need for further studies that

TABLE 1. *Biotypes of Brucella melitensis.*

Reference	Total isolates (N)	Biotype 1 (N)	Biotype 2 (N)	Biotype 3 (N)
Corbel [9]	53	22	30	1
Qadri [2]	146	94	0	52
Eltigani [1]	175	56	79	40
Bilal [3]	70	0	0	70
Total	444	172	109	163

may aid in the discovery and clarification of epidemiological linkages. Unfortunately, in the countries most affected by brucellosis, including Saudi Arabia, biotyping has not been performed to such a level so as to provide worthwile epidemiological evaluation.

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Unilateral Spontaneous Adrenal Hemorrhage During ACTH Treatment of Multiple Sclerosis

To the Editor: Spontaneous adrenal hemorrhage is uncommon. Septicemia, anticoagulation and stress are the most commonly associated predisposing factors.

We report a rare case of unilateral adrenal hemorrhage which occurred in a young female patient suffering from multiple sclerosis and being treated with a pinfusion of adrenocortico-trophic hormone. The diagnosis was made clinically, documented by echography and confirmed at laparotomy. A review of the literature and discussion follows.

A 27-year-old female suffering from multiple sclerosis for 18 months was admitted to the hospital because of a relapse of her neurologic symptoms. An ACTH infusion was given with a dose of 120 units per day. We were called to see the patient 36 hours after the beginning of the infusion because of severe right flank pain. On examination she had right costovertebral angle tenderness, there was no guarding or rebound tenderness. Auscultation of the abdomen was normal. Hematocrit was 38%, WBC was normal. Our differential diagnosis was a right adrenal hemorrhage, right kidney colic, or an unusual presentation of appendicitis.

An abdominal ultrasound was performed and showed right suprarenal collection compatible with an adrenal hemorrhage.

A laparotomy was performed and a large retroperitoneal hematoma was found with a partially ruptured 6 cm tense hematoma of the right adrenal. The right adrenal was removed and hemostasis was satisfactory. The left adrenal was normal. Histopathologic examination confirmed recent adrenal hemorrhage. The patient had a noncomplicated postoperative course, two months later an endocrine work-up showed a normally functioning left adrenal.

Spontaneous acute adrenal hemorrhage is a rare clinical presentation. It is associated with a high morbidity and mortality rate.

Unilateral adrenal hemorrhage may present with acute costovertebral angle pain mimicking a kidney colic, unusual site of appendicitis or psoas muscle disease [1].

Because the contralateral adrenal was intact in our patient, there were no signs of acute adrenal insufficiency. Also because of persistence of contralateral adrenal function, hyponatremia, hyperkalemia, are not a part of the biochemical presentation, hypotension and acute anemia could be secondary to hemorrhage and not hormonal deficiency. The diagnosis can be documented by echography or computed axial tomography scan (CAT), both of which can show the adrenal hematoma [2–4].

In the literature, adrenal hemorrhage has been secondary to anticoagulant therapy [2], infections [5], neoplasia [6], stress [7], in the post-partum [8,9], following idiopathic unilateral vein thrombosis and a complication of venography. Adrenal hemorrhage has been described secondary to abdominal or intracranial tumors, surgery, or trauma [5–7,10,11].

The Waterhouse-Friderichsen syndrome secondary to fulminant meningococcemia involves an acute hemorrhagic destruction of both adrenal glands [12]. Syphillis [13] has been the cause of adrenal hemorrhage as well as a rare form described in the newborn.

ACTH has been implicated in the adrenal hemorrhage.

Shaberg et al [14] showed cortical hemorrhages in guinea pigs with ACTH, Wilbur and Rich [15] demonstrated degeneration of renal tubules in rats given ACTH.

Wilson et al [16] described adrenal apoplexy occurring during corticotropin therapy of ulcerative colitis.

Galin [17] also reported unilateral adrenal hemorrhage during ACTH therapy.

Marcus et al [18] reported bilateral adrenal hemorrhage during ACTH treatment of ulcerative colitis.

Gjorup et al [19] reported massive adrenal hemorrhage following treatment with corticotropin hormone.

The common factor in adrenal hemorrhage is the stimulation of the adrenal glands either by endogenous ACTH secondary to stress or by exogenous ACTH.

In our patient, and in the few unilateral adrenal hemorrhages reported secondary to ACTH administration, we do not have an explanation for the one sided hemorrhage.

A rare case of unilateral adrenal hemorrhage was presented secondary to ACTH administration for multiple sclerosis. This diagnosis is to be considered in ACTH-treated patients as well as spontaneously.

Medical or surgical treatment is to be considered according to clinical, biological and radiological follow-up.

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Cimetidine in Children with Peptic Esophagitis

To the Editor: I refer to the paper "Gastroesophageal reflux in infants and children" by El-Mouzan [1]. The author states that "H_2 antagonists, such as cimetidine inhibit gastric acid secretion and therefore may help in the treatment of esophagitis."

This is of course correct. However, the evaluation of the H_2 antagonists and statement regarding cimetidine side effects are misleading. Cimetidine is the only H_2 antagonist which is recommended for children precisely because safety and efficacy are established. Ranitidine, famotidine and nizatidine are not recommended for use in children because efficacy and safety have not been established.

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Reference

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Reply

To the Editor: The statement referred to in Dr. O'Sullivan's letter reads: "The drug (cimetidine) has potentially serious side effects and should not be considered for prolonged use in children ...." [1].

Although some physicians might not agree with such statements, there remains a fact that none of the available H_2 antagonists have been fully evaluated in clinical trials involving children to proclaim safety for long-term use and this is appropriately acknowledged both in the literature and in the drug information brochures of Tagamet (cimetidine) by SmithKline Beecham and Zantac (ranitidine) by Glaxo. Accordingly, it is appropriate not to recommend the long-term use of these drugs in children with gastroesophageal reflux with the understanding that short causes of H_2 antagonists have been successfully used without serious problems.

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1. El-Mouzan MI. Gastroesophageal reflux in infants and children. Ann Saudi Med 1991;11(2):152-8.

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

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Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

Third International Course on Magnetic Resonance Imaging, Riyadh Armed Forces Hospital

The Third International Course on Magnetic Resonance Imaging will be held from 25 to 28 October 1992 (25 Rabi Al-Thani to 3 Jumada Al-Awal 1413). For further information, please contact: Riyadh Armed Forces Hospital, Department of Medical Studies, P.O. Box 7897, Riyadh 11459, Saudi Arabia. Tel.: (966) (01) 477-7714, extensions 2289/2269; Fax: (9661) 477-7194/477-9168.

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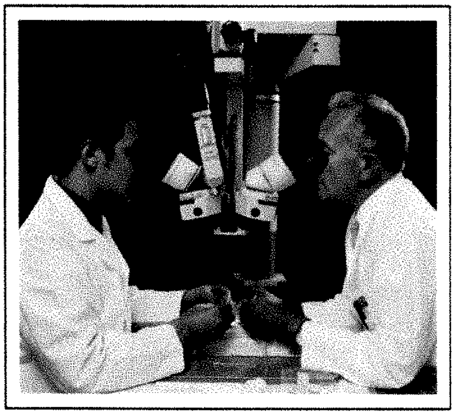

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المجلد ١٢ العـدد٣ شوال ١٤١٢هـ مايو ١٩٩٢م

المدونـات الطبيـة السعوديـة

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مساعدتا التحرير:

فرجينيا جي كروزير
شيرلي موفيت

المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي ـ جامعة الملك سعود، صندوق بريد ٢٩٢٥ ـ الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ ـ الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوَّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي:

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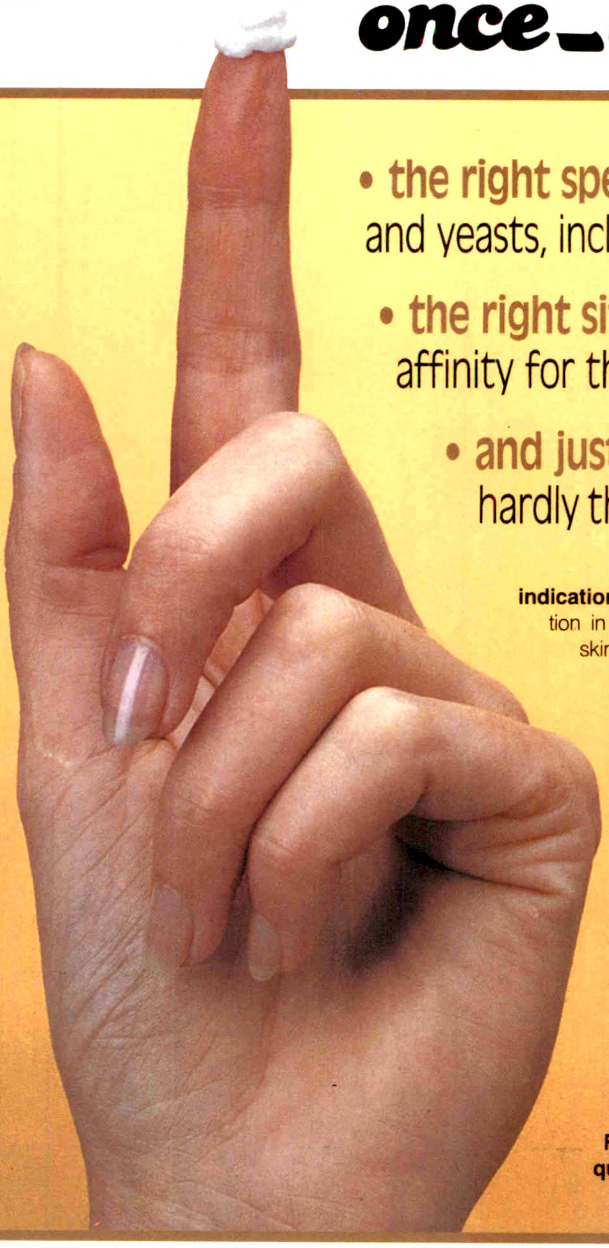

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ANNALS OF SAUDI MEDICINE

Aims and Scope

The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

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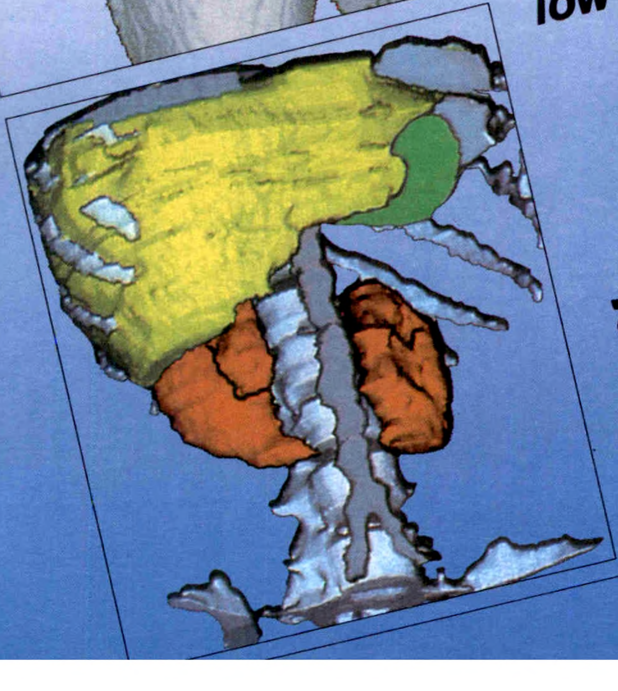

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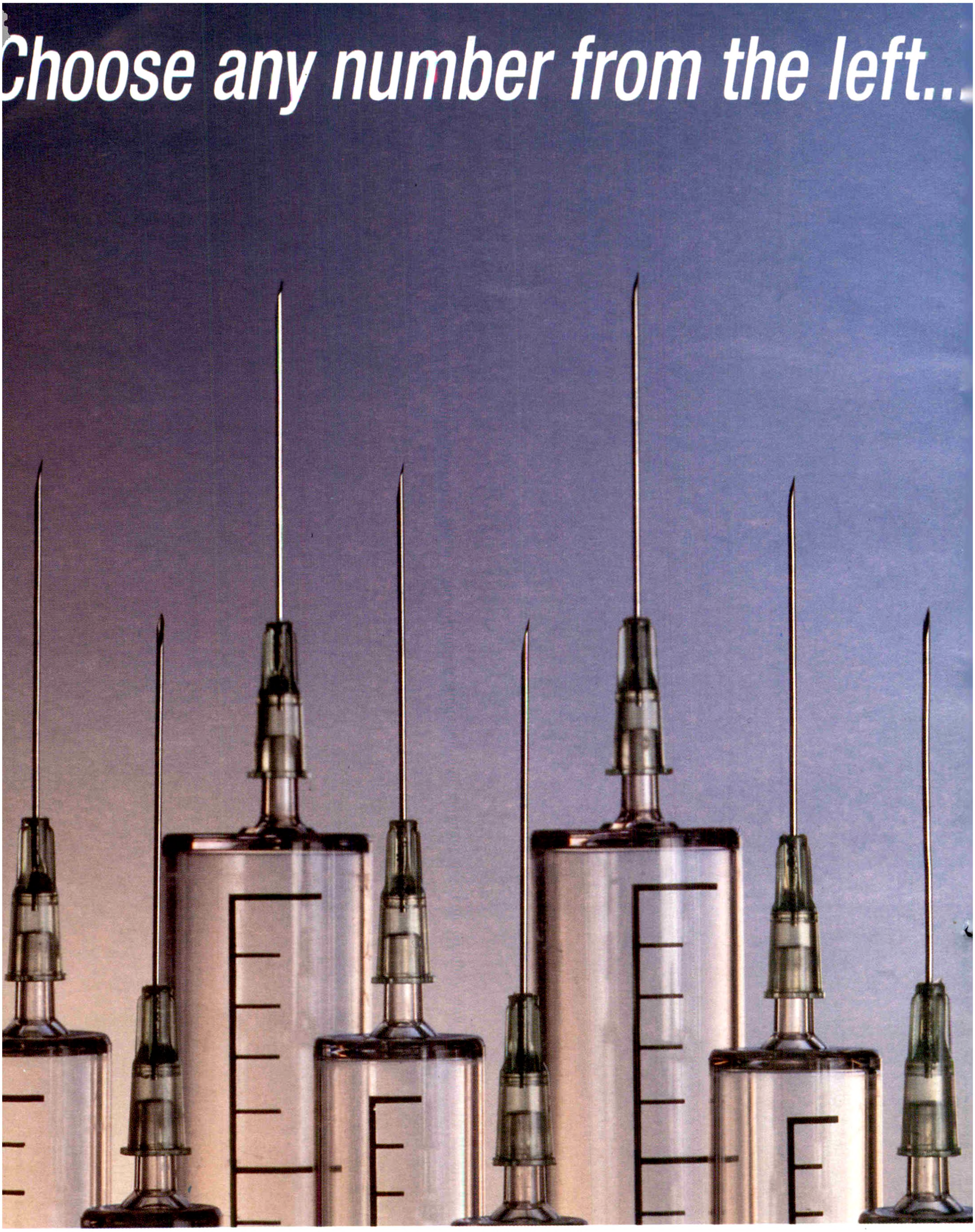

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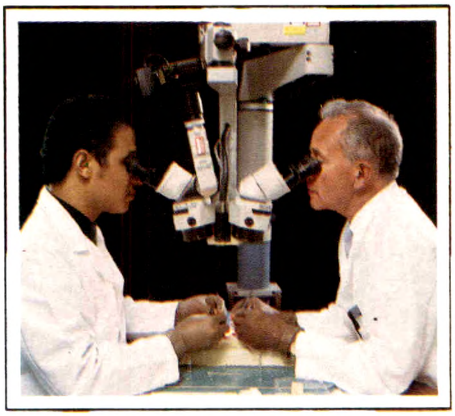

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Editorial

TOWARDS MINIMAL INVASIVENESS IN SURGERY

In March 1988 I presented an Editorial in the *Annals of Saudi Medicine* eulogizing about the remarkable changes which had occurred in the field of urology while at the same time debating "therapy with the knife: is it still needed for renal stones?" At that time I did not intend to imply that the surgical blade had grown obsolete but only that the ancient art of "cutting for stone" had come of age and was passing us by. It now appears that technology has rushed through urology and other specialities such as orthopedics and cardiovascular surgery, rendering these specialties unrecognizable from the surgical disciplines we once knew a few years ago and have finally laid siege to the die-hard conservative stronghold of the general surgeon. The knife, indeed, is now in danger of becoming extinct.

The main theme of these technological advances has been to replace radical, often mutilating, surgical procedures with minimal invasive techniques that achieve the same end. Judged in terms of morbidity and hospitalization stay, the results are certainly superior and their very minimal-invasiveness lends the new techniques a further advantage, that of almost infinite repeatability should the disease process recur. The old surgical adage decrying "key-hole surgery", with the truism that surgical wounds heal from side-to-side and not from end-to-end, is now to be scorned. Modern optics allow elaborate and effective endoscopic surgical manipulation in an increasing number of body organs through one or more skin entry key-holes. The list of procedures grows daily: percutaneous nephrolithotomy and even nephrectomy, gastroduodenoscopy, arthroscopy, endoscopic hysterectomy, tubal ligation, mediastinoscopy, thoracoscopy and thoracoscopic lobectomies, pelviscopy with lymph node sampling prior to major pelvic surgery, and various laparoscopic general surgical procedures. Once rare trial achievements, all of these procedures have now become routine tools in the surgical armamentarium and most are available in hospital centers within the Kingdom of Saudi Arabia.

Numerous other factors have helped to promote the trend toward non-surgical treatment of erstwhile "surgical diseases": a better understanding of the pathology and natural history of disease processes, improved imaging techniques and functional evaluation in investigation, advances in chemotherapy for tumors, sophisticated technology and above all else, the greater acceptance of the multidisciplinary team approach in management. To date, we have witnessed the slow evolution of treatment in surgical oncology, especially from a radical approach to a conservative approach. For example, Halstead's notoriously mutilating radical surgery for carcinoma of the breast has been modified over the years until quite recently when it became acceptable to perform a simple mastectomy but now, a mere local excision of a malignant lump (lumpectomy) is performed. Even the classical standard of radical nephrectomy as treatment for renal cell carcinoma is under challenge: many surgeons now accept simple nephrectomy as being adequate and most are in agreement that partial nephrectomy is good treatment for a tumor in a solitary kidney or when tumors present bilaterally. Chemotherapy has produced a spectacular improvement in the results of treatment of many tumors, e.g., malignant testicular teratoma, safegarding patients from major surgical procedures.

Many patients with myocardial ischemic disease who would have previously been candidates for coronary artery bypass surgery are now being successfully treated with balloon angioplasty and those with mitral valve stenosis are responding similarly to percutaneous transarterial catheter balloon dilatation. Operations can now be performed with needles and catheters where previously open surgery was required. A few examples of several of these procedures include percutaneous nephrostomy, percutaneous drainage of intra-abdominal abscesses, and percutaneous transhepatic biliary drainage and stenting. Many advanced applications of new percutaneous techniques have been made possible by enhanced imaging technology using ultrasound, computerized tomographic (CT) scanning and biplanar x-ray fluoroscopy, supported by a variety of surgical endoscopic facilities, including diathermy, dormia and forcep extractors, ultrasonic lithotripsy and laser beam. A new breed of interventional radiologists have grown up with these techniques, establishing close working relationships with clinicians and becoming involved in the direct management of patients.

The urologist is justly proud at spearheading and being at the forefront of these advancing minimally-invasive surgical techniques. The first endoscopes were developed and applied to urological procedures in the lower urinary tract and to date, there remains no recess in the upper or lower urinary passages which are inaccessible to direct endoscopic examination and instrumentation. Very few enlarged prostates, bladder tumors or stones, which together make up more than two-thirds of all urological lesions necessitating intervention, now require open surgery. The combination of endourology and extracorporial shockwave lithotripsy (ESWL) has virtually eliminated the need for open surgery for all kinds of urinary tract stones. The young urological trainees may never see a lower third ureterolithotomy! The same techniques, and in many instances the same instruments, have spilled over in application to other surgical specialities. The ultimate non-invasive tool in treating urinary tract stones, ESWL has also found application, albeit in a limited way, in the treatment of other stones elsewhere—in the salivary ducts or biliary tract. Cholecystectomy as the only treatment for the gallbladder containing gallstones has now been challenged. Approximately 15–25% of patients with gallstones are currently considered suitable for ESWL or percutaneous cholecystolithotomy. The previously feared specter of the retained common bile duct stone (CBDS) following surgery, however, has now been eliminated by the rescue at postoperative endoscopic instrumentation by ERCP or by ESWL. The classical indications in exploring CBD may not remain classical!

The general surgeon has been late in adapting endoscopic techniques to abdominal surgery, probably because all the body orifices have been occupied by somebody else. The development and extending applications of flexible gastroduodenoscopy were left contentedly in the hands of the gastroenterologist and, despite the readily availability of the peritoneal cavity for endoscopic access to virtually all abdominal organs, the laparoscope too, was left initially for the gynecologist to explore. The development of the surgical abdominal laparoscope, however, has opened up a fascinating new Ali Baba's Cave to the general surgeon. Laparoscopic cholecystectomy (or "lap chole" as it is now termed) is beginning to replace the standard open procedure—one of the most frequently performed operations in surgical practice—and the vista of other intra-abdominal applications is tantalizing: ligation of varicocele, hernia repair, removal of the abdominally-retained testis, gastrectomy, Hiller's operation, vagotomy and highly selective vagotomy, the abdominal portion of esophagectomy, hemicolectomy, laparoscopic examination and biopsy of various abdominal masses and division of adhesions. Many of these laparoscopic procedures have already been pioneered in a few centers, but the day is not far away when these procedures may be expected to become standardized.

With all these promises of minimally invasive surgery, we must not lose sight of the need for weighing each new technique against the standard now available, of the need for evaluating results objectively and the need for proper training of those who will perform the new procedures. The surgeon should resist the temptations and pressures from the media, from patients, and the industry in undertaking any new modalities without proper evaluation and adequate training.

As Saudis, we should be proud that many of these new technologies are rapidly becoming standardized in our hospitals and are freely available to all patients. The wave of new technology in tertiary care should not, however, blind us to the equally important requirement of undertaking epidemiological studies and developing primary health care services.

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Original Articles

IS INTRAVENOUS UROGRAPHY MANDATORY IN THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA?

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تم تصوير السبيل البولي بالحقن الوريدي (IVU) وتخطيط الصدى (US) لدى أربعة وخمسين مريضًا يعانون من فرط التنسج الموثي الحميد (BPH) وذلك لملاحظة فوائد تصوير السبيل البولي بالحقن الوريدي IVU مقارنة بتخطيط الصدى US . كانت المعالم التي استخدمت اكتشاف شواذ في أعلى السبيل البولي في كلتا الوسيلتين، وأثر الانطباع الموثي الإشعاعي RPI على طريقة الجراحة، ومقارنته بحجم الموثة مقدرًا بالأصبع DEP . تمت مقارنة كل من الإنطباع الموثي الإشعاعي والحجم الموثي مقدرًا بالأصبع مع وزن الورم الغدي (AW) . كان ترابط الانطباع الموثي الإشعاعي RPI والحجم الموثي مقدرًا بالأصبع DEP ممتازًا (٨٧,٥٪) في الدرجة الثالثة، إلا أنه كان ضعيفًا في الدرجتين الأولى والثانية. وكان ترابط الانطباع الموثي الإشعاعي ووزن الورم الغدي (AM) . كان ترابط الانطباع الموثي الإشعاعي ووزن الورم الغدي AM جيدًا في الدرجة الثالثة (١٠٠٪)، وكان واضحًا أيضًا في الدرجتين الأولى والثانية، فيما كان ترابط الحجم الموثي مقدرًا بالأصبع DEP مع وزن الورم الغدي AW جيدًا في جميع الدرجات. أمكن باستخدام الانطباع الموثي الإشعاعي RPI والحجم الموقي مقدرًا بالأصبع DEP التكهن بطريقة استئصال الموثة بشكل دقيق في الدرجتين الأولى والثالثة، فيما كان الانطباع الموثي الإشعاعي أفضل هامشيًا في التكهن بهذه الطريقة، لم تكن هناك شواذ في أعلى السبيل البولي أمكن اكتشافها بتصوير السبيل البولي بالحقن الوريدي (IVU) ولم يمكن اكتشافها بتخطيط الصدى US . نخلص إلى القول بأن تصوير السبيل البولي بالحقن الوريدي لا يضيف أية معلومات جديدة فوق ما يظهره الفحص المستقيمي وتخطيط الصدى مما قد يغير المسار الجراحي. لذا فأنه في الحالات غير المختلطة من فرط التنسج الموثي الحميد يجب التساؤل عن جدوى الاستخدام الروتيني لتصوير السبيل البولي بالحقن الوريدي في المملكة العربية السعودية.

Fifty-four consecutive patients with uncomplicated benign prostatic hyperplasia (BPH) underwent intravenous urography (IVU) and ultrasonography (US) to observe the benefits of IVU over US. The parameters used were upper tract abnormalities detected on both modalities and the influence of radiological prostatic impression (RPI) on the route of surgery and its comparison to digitally estimated prostatic size (DEP). Both RPI and DEP were compared to the adenoma weight (AW). Correlation of RPI and DEP was excellent (87.5%) in grade III but poor in grades I and II. RPI and AW correlated well in grade III (100%) and was also significant in grades I and II, whereas DEP correlated well with AW in all grades. Both RPI and DEP could predict the route of prostatectomy accurately in grades I and III, whereas in grade II, RPI was marginally better in predicting the route. There was no upper tract abnormalities that were detected on IVU and missed by US. In conclusion, IVU did not add any additional information beyond that obtained by rectal examination and US to alter the surgical approach and hence the routine use of urography in uncomplicated BPH should be questioned in Saudi Arabia.

Benign prostatic hyperplasia (BPH) is the most common urological problem in patients over the age of 60-years. Approximately 20% to 25% of men over the age of 50-years may require prostatic surgery [1]. IVU has been commonly performed prior to surgery; the rationale of which is debatable. In developed countries, the use of IVU as a preoperative investigation in BPH management is dwindling due to the lack of additional information obtained and infrequent upper tract pathology [2–6]. In developing countries around the

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Middle East, even though the health care is fairly extensive, the elderly male population may not have had adequate medical care throughout their lives and hence there may be undetected upper tract disease. For example, bilharziasis is rampant in the Middle East and could afflict the elderly population and may remain asymptomatic. We have therefore evaluated 54 men undergoing treatment for uncomplicated BPH to see if IVU is mandatory to detect any upper tract abnormality and to see if it has made any significant contribution to the treatment plan. Traditionally, the need for IVU was assessed by the upper tract abnormality detected [2]. However, in addition to this, we have assessed the RPI seen on IVU films with the DEP and with the route of prostatectomy.

Material and Methods

Fifty-four consecutive patients presenting with acute retention of urine and prostatism were included. Patients with BPH, and elevated creatine, microscopic, and macroscopic hematuria have been excluded. All patients underwent IVU, US, and digital rectal examinations.

The rectal examination assessed the size of the prostate gland by comparing it to an inflated Foley balloon. The size was graded as: up to 24 ml grade I, 25 to 60 ml grade II, and > 60 ml grade III. Any IVU abnormality of the upper tract was noted especially stones, hydronephrosis, renal cysts, and fish hook deformity of the lower ure-ters. The RPI seen in a 30 minute IVU film was presumed to represent the upper part of the prostate and this was measured from the pubic symphysis. The IVU was performed under the supervision of a radiologist and constant position of the patient and the x-ray tube was achieved in all cases to prevent alterations in size of the RPI which was graded as follows: grade I up to 2 cm, grade II 2.1 to 4 cm and grade III > 4 cm.

At cystoscopy, the length of the prostatic urethra, size of the middle and lateral lobes including the intravesical extension, trabeculae and diverticulae were noted. The gland (either TUR or open) was weighed immediately following surgery. All prostatectomies were performed by consultants. The TUR weight was multiplied by a factor of 1.3 to compensate for the loss of tissue due to diathermy [7].

The IVU and US findings were compared. RPI was compared to DEP and AW. The type of surgical approach was correlated with RPI and DEP. In 15 patients, fish hooking of the lower ureters was also studied in relation to AW, RPI, and route of prostatectomy.

Results

I. *Correlation of IVU and US findings (Table 1)*
Six patients had hydronephrosis and two had renal stones detected both by IVU and US. Of five patients with renal cysts on US, only four were detected by IVU.

II. *Correlation of RPI and DEP (Table 2)*
Correlation was excellent in grade III (87.5%) and was poor in grades I and II (53% and 48%, respectively).

III. *Correlation of AW and RPI (Table 3)*
Correlation was excellent (100%) in grade III and was significant in grades I and II.

IV. *Correlation of DEP and AW (Table 4)*
Correlation was almost 70% in all grades.

V. *Correlation of RPI with surgical approach (Table 5)*
All patients in grade I, 9/9 (100%) had TUR, 23/24 (96%) in grade III had open prostatectomy. In grade II, 15/21 (71%) had TUR.

VI. *Correlation of DEP and surgical approach (Table 6)*
All patients 15/15 (100%) in grade I had TUR, 16/16 (100%) in grade III had open prostatectomy. In grade II, 10/23 (43%) had TUR.

Fish Hooking

Fish hooking of lower ureters was seen on urography in 15 patients. Of these, ten had enlargement of the middle lobe. In only two patients, the middle lobe weighed between 30% to 40% of the total gland weight and in the remaining eight patients it was small and only weighed between 8% to 16% of the total weight. The mean weight of the prostate gland in these patients with fish hooking was 78 gm (range 36 to 243 gms). Judging by RPI, fish hooking was present in 12/15 (80%) in grade III and 3/15 (20%) in grade II. Because of the large size of the gland, most 14/15 (93%) had open prostatectomy. It was also noted that the prostatic urethra at cystoscopy was long (4 to 7 cm) and intravesical enlargement of the lateral lobes was present in all of them.

Table 1. *IVU and US findings.*

Upper tract abnormalities	IVU	US
Hydronephrosis	6	6
Renal cysts	4	5
Renal stones	2	2
Normal	42	41
Total	54	54

IVU = intravenous urography; US = ultrasonography.

Table 2. *Correlation of RPI and DEP.*

	Rectal Exam Grades as estimated radiologically		
Grades	Within range	Outside range	Total
I	8 (53%)	7 (47%)	15
II	12 (52%)	11 (48%)	23
III	14 (87.5%)	2 (12.5%)	16
Total			54

RPI = radiological prostatic impression; DEP = digitally estimated prostatic.

Table 3. *Correlation of accurate AW and RPI.*

	Grades as estimated radiologically			
Adenoma Wt (gm)	Grade I up to 2 cm	Grade II 2.1–4 cm	Grade III up to 4 cm	Total
25 gm	8 (67%)	4 (33%)	0	12
25–60 gm	1 (4%)	17 (68%)	7 (28%)	25
>60 gm	0 (0%)	0 (0%)	17 (100%)	17
Total				54

AW = adenoma weight; RPI = radiological prostatic impression.

Table 4. *Correlation of accurate DEP and AW.*

Adenoma	Rectal exam			
Wt (gm)	Grade I	Grade II	Grade III	Total
25 gm	11 (73%)	4 (27%)	0	15
25–60 gm	0	16 (69.5%)	7 (31.5%)	23
>60 gm	0	5 (31%)	11 (69%)	16
Total				54

DEP = digitally estimated prostate; AW = adenoma weight.

Table 5. *RPI and surgical approach.*

Radiological Grading	TUR	Open	Total
I	9 (100%)	0	9
II	15 (71%)	6 (29%)	21
III	1 (4%)	23 (96%)	24
Total			54

TUR = transurethral resection; RPI = radiological prostatic impression.

Table 6. *DEP and surgical approach.*

DEP	TUR	Open	Total
Grade I	15 (100%)	0	15
Grade II	10 (43%)	13 (57%)	23
Grade III	0	16 (100%)	16
Total			54

DEP = digitally estimated prostatic; TUR = transurethral resection.

Discussion

IVU, once a gold standard for evaluation of BPH has now been withheld as a superfluous investigation with the availability of US. Even today, ionic contrast media is routinely used for IVU and it still has a mortality of 1:75,000 in addition to other side effects such as anaphylaxis, skin rash, and rhinorrhea [8]. Although recent low osmolar non-ionic contrast media is much safer because of the high cost, its use is mainly restricted for myelography which requires only a small dose [9]. IVU also consumes a lot of imaging time for a busy radiology department. The use of IVU in early days of urological surgery was to evaluate bladder trabeculation, residual urine, diverticulae, lower ureteric hooking and prostatic impression as well as the upper tract abnormalities. However, the advance and availability of real time US imaging provides a comparable assessment of upper tract such as parenchymal integrity and dilatation of the collecting system. Moreover, US of the bladder evaluates diverticulae and residual urine. Prostatic size can also be accurately measured using a rectal probe. However, in certain parts of the world such as the Middle East where bilharziasis or stones are common, it may be expected to observe such problems in this patient age group. However, our evaluation shows that there were few significant upper tract diseases in this age group and both IVU and US may detect these abnormalities. In addition, we have assessed the RPI and compared it with DEP and AW. The route of surgery was also compared in both RPI and DEP. Our results suggest that RPI correlated well with DEP in grade III (87.5%) but was poor in grades I and II. RPI correlated well with AW in grade III (100%) and was also equally significant in grades I and II (67% and 68%, respectively). However, DEP correlated well with AW in all grades (70%). Both RPI and DEP could predict the surgical approach accurately in grades I and III. However, grade II seems to be a gray area where both RPI and DEP are inadequate tools for accurate prediction although the former seems to be marginally better. Grade II is also a group where the route of surgery depends upon the experience of the surgeon. An experienced surgeon would proceed with a TUR for this grade. Fish hooking of the ureters although previously thought to be due to the enlargement of the middle lobe [10], seems to be due to the intravesical enlargement of the lateral prostatic lobes. RPI as such is mainly caused by lateral lobar enlargement and to a lesser extent by the middle lobe. However, this information obtained at urography adds little to the management of patients as far as surgical approach is concerned. The infrequent upper tract abnormalities seen on IVU, side effects, cost and time consumption makes it an unnecessary investigation even in tropical countries. Most of the information regarding the prostate and upper tract may be obtained by clinical examination, KUB, US, and cystoscopy.

We conclude that IVU did not have any additional benefit either in detecting upper tract disease or supplement information requiring a change of treatment plan. Hence, US should replace the routine use of IVU in management of uncomplicated BPH. In addition, ultrasound is the investigation of choice even in patients with impaired renal function due to BPH.

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MALIGNANT NEOPLASIA OF THE COLON, RECTUM AND ANUS AT THE KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

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تعتبر الأورام الخبيثة في القولون والمستقيم والشرج غير شائعة نسبيًا في المملكة العربية السعودية. يدون هذا المقال المعلومات الأساسية الواردة في قاعدة بيانات سجل أورام القولون والمستقيم بمستشفى الملك فيصل التخصصي ومركز الأبحاث. تم تسجيل ٦٢٢ مريضًا في الفترة بين شهر يونيو ١٩٧٥م وشهر ديسمبر ١٩٨٩م على أنهم مصابون بأورام خبيثة في القولون والمستقيم والشرج. كان عدد الذكور ٣٨٣ والأناث ٢٣٩. ومتوسط أعمارهم ٥٣,٥ عامًا و ٤٧,٨ عامًا على التوالي. كان معظم المرضى سعوديين. كان موقع الإصابة الأصلية الأكثر تواردًا في الأمعاء الغليظة هو المستقيم. تبين وجود ٤٥٥ حالة من الأورام الغدية السرطانية البسيطة، و ٣٩ حالة من الأورام الغدية السرطانية المخاطية، و ١٧ جالة من الأورام الغدية السرطانية من نوع Signet - Ring، ٤٦ حالة من السرطانات البشروية. كانت معظم الأورام معتدلة التمايز وكانت أقطار غالبية الأورام تزيد عن ٥ سم. تركزت الآفة في ٥٧ مريضًا في العضو الأصلي. بينما بدأت الآفة في ٥٦ مريضًا في العضو الأصلي ولكنها انتقلت مباشرة إلى العضو المجاور، أما بقية المرضى فقد كانوا يعانون إما من انتشار قاص للآفة أو انتشار عقدي. أتت الغالبية العظمى من المرضى إما من مكة المكرمة أو من الرياض. لا توجد فروق اقليمية فيما يتعلق بالداء. كانت الآفات أصغر وأكثر تمايزًا في القولون السيني مقارنة بالمستقيم أو القولون الأيمن إلا أن عدد المرضى المصابين بآفات انتقالية في العقيدات أو الأعضاء القاصية كان أكثر. كانت الأورام لدى قدوم المريض أصغر حجمًا وأقل انتشارًا في المرضى السعوديين مقارنة بالمرضى العرب الآخرين.

Malignant neoplasms of the colon, rectum, and anus are relatively uncommon in the Kingdom of Saudi Arabia. This paper documents the King Faisal Specialist Hospital and Research Centre tumor registry colorectal cancer data base. Between June 1975 and December 1989, 622 patients were registered with malignant colorectal and anal tumors. There were 383 males and 239 females. The average ages were 53.5 years and 47.8 years. The majority of patients were Saudi. The single most common site for large bowel malignancy was the rectum. There were 455 simple adenocarcinomata, 39 mucinous adenocarcinomata, and 17 signet-ring adenocarcinomata. There were 46 epidermoid cancers. Most of the tumors were moderately differentiated and the majority of tumors were greater than 5 cm in diameter. Fifty-seven patients had disease localized to the organ of origin, 56 patients had disease which was localized but directly invading an adjacent organ, and the remaining patients had nodal or distant spread. The greatest majority of patients came from either Makkah or Riyadh. There were no provincial differences in the disease. There were more smaller and differentiated lesions in the sigmoid colon than in the rectum and right colon, but more patients with metastatic disease to the nodes or distant organs. Tumors were smaller at presentation and less disseminated in Saudis than in the other Arabs.

Although some differences exist between the disease in the Kingdom of Saudi Arabia (KSA) and "West", it would appear from this relatively large study that, in general, the disease is similar to the disease that has been described elsewhere. It is felt that the present series is representative of the disease in Saudis at the present time and that it may be used as a basis for further prospective studies in the future.

Malignant neoplasms of the colon, rectum, and anus are relatively uncommon in the Kingdom of Saudi Arabia (KSA). The King Faisal Specialist Hospital and Research Centre (KFSH&RC) is a

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national referral hospital and the principal center for cancer therapy in the KSA. The King Faisal Specialist Hospital Tumor Registry opened in June 1975 and malignant tumors of the large bowel and anus were the 14th most common tumors registered (3.3%). Although the tumor registry is not population based, the hospital is the primary cancer referral institution in the KSA and, therefore, the registry probably documents the majority of oncology patients in the KSA. The colorectal section of the tumor registry thus presently represents the disease in the KSA better than any other data base and is probably the largest in the KSA. This paper attempts to document the tumor registry colorectal cancer data base.

Many of the patient data sets were incomplete so that information was missing with respect to grade, tumor size, and stage in some patients.

Material and Methods

Colorectal tumor registry data was down loaded on to PC floppy disk and then converted for analysis on a Macintosh IISi using "Clinibase" [1]. Patients race, tumor site, histopathology, degree of differentiation, tumor size, stage, and province of origin were analyzed.

Results

General

Six hundred twenty-two patients were registered with malignant colorectal and anal tumors. There were 383 males and 239 females. The average ages were 53.5 years and 47.8 years, respectively. The majority of patients were Saudis (Table 1). There were seven "Western" patients.

The single most common site for large bowel malignancy was the rectum. An approximate equal number of patients were registered with right-sided tumors and sigmoid colonic tumors (Table 2).

There were 455 simple adenocarcinomata, 39 mucinous adenocarcinomata, and 17 signet-ring adenocarcinomata. There were 46 epidermoid cancers and a variety of other rare histological types (Table 3). Two patients were found to have carcinoma in situ (left colon) and three patients were found to have carcinoma in an otherwise

TABLE 1. *Race.*

Race	Number
Saudi	538
Yemeni	24
Lebanese	20
African	7
Egyptian	10
American	7
Indian/Pakistani	8
Other Arab	2
Other	6

TABLE 2. *Site according to ICD code.*

Site	Number
Appendix	11
Cecum	59
Ascending colon	30
Hepatic flexure	10
Transverse colon	18
Splenic flexure	9
Descending colon	21
Sigmoid colon	61
Colon (other)	15
Colon (nos)	43
Rectosigmoid	42
Rectum	248
Anal canal	22
Anus	19
Rectum (other)	14

TABLE 3. *Histology.*

Histology	Number
Carcinoma in situ	2
Adenocarcinoma	455
Adenocarcinoma in villous adenoma	3
Anaplastic	1
Mucinous	79
Signet-ring	17
Squamous	2
Epidermoid	46
Melanoma	2
Lymphoma	5
Basiloid	3
Cloacogenic	3
Carcinoid	1
Leiomyosarcoma	3

benign polyp—all in villous tumors situated in the rectum. Most of the tumors were moderately differentiated (Table 4) and the majority of tumors (Table 5) were greater than 5 cm in diameter. Fifty-seven patients had disease localized to the organ of origin. Fifty-six patients had disease which was localized but directly invading an adjacent organ and the remaining patients had nodal or distant spread.

The greatest majority of patients came from either Makkah or Riyadh (Table 6).

TABLE 4. *Grade (differentiation).*

Grade	Number
Well	32
Moderately	245
Poor	127
Undifferentiated	10

TABLE 5. *Tumor size.*

Size	Number
0–0.9 cm	0
1–1.9 cm	8
2–2.9 cm	1
3–3.9 cm	7
4–4.9 cm	8
5–5.9 cm	14
6–6.9 cm	13
7–7.9 cm	10
>8 cm	12

TABLE 6. *Tumor registry region.*

Region	Number
Asir	34
Baha	8
Eastern	80
Hail	18
Jawf	3
Jizan	20
Medina	36
Makkah	107
Najran	11
Northern	5
Qasim	32
Qurayat	2
Riyadh	245
Tabouk	5
Yemen	4
Other	11

Site of Disease

Patients seemed to be older at presentation as tumors were situated in the right colon, sigmoid colon, and rectum. There was no difference in histopathology or staging at the various sites examined although there did seem to be more differentiated lesions in the sigmoid colon (80% compared with 73.3% in the rectum and 60% in the right colon). Thirty percent of tumors were greater than 6 cm in diameter in the sigmoid colon whereas tumors of this size accounted for 50% of the tumors in the rectum and right colon. Patients with metastatic disease to the nodes or to distant organs at the time of presentation accounted for 47.1% of sigmoid lesions whereas only 23.8% and 25% of right-sided and rectal lesions were associated with metastatic disease.

Race

The site, differentiation, and histopathology seemed to be the same in Saudis and other Arabs (Yemeni, Lebanese, and Egyptian). Tumors, however, were smaller at presentation and less disseminated in Saudis than in the other Arab people (42.2% Stage I compared with 22.7% Stage I in the other Arabs).

Region

There did not appear to be any differences in the disease in the two centers in which the largest number of patients (Riyadh and Makkah) were registered.

Grade

Six and one-half percent of either poorly differentiated or undifferentiated tumors were in the sigmoid colon whereas 33.6% of these tumors were in the rectum. Conversely, 13.7% of well or moderately differentiated tumors were in the sigmoid colon whereas 45% were situated in the rectum.

Discussion

While this is the largest series of patients with colorectal malignancy reported from the KSA, it is difficult to know exactly how representative it is because of the problem of referral bias. Although the KFSH&RC received the majority of patients with cancer in the past, as other large hospitals have become established, it is likely that increasing numbers of patients with this disease, especially those with localized disease, have been managed at other hospitals elsewhere in the KSA. This would bias the data in favor of late disease but it might also be argued that the very sick are not referred to the hospital because they are not able to be treated and so the series is biased in favor of early disease. Many advanced patients were, however, referred to the hospital and in fact, in general terms the disease stage at registration, (32.4% with metastatic disease) was quite advanced. There have been no published series to support the idea that localized disease is not referred to the KFSH&RC and data from other institutions tend to have the same case mix [2] as our own. On balance, it seems likely therefore that the present series is representative of the disease as it is in the KSA at the present time.

More Saudis (86.5%) in comparison with other Arabs were referred to the KFSH&RC than to Riyadh Central Hospital (RCH) (54%) so that this series is more likely to reflect the true state of the disease among Saudi patients than other reports [2].

The follow-up of patients at the KFSH&RC has been poor because of poor patient compliance. Survival data do not exist and this does not seem to be unique to this series [2].

The male to female ratio (1:0.62) was higher in this series than in the "West" where ratios of 1:0.9 are usually reported [3]. The lower numbers of Saudi females registered with right-sided tumors has been documented before (in press) and may in part explain the high ratio found in the present series. Patients registered in the KSA tended to be younger at the time of their registration in comparison with the "West" [3,4] and this may simply be a function of the general population age structure [5].

The rectum was the single most common site for colorectal cancer in the present study. A similar rectal preponderance has been reported previously from the KSA [2] and in the "West" [6]. Mucinous (14.3%) and signet-ring (3.1%) variants of adenocarcinoma were similar in frequency to those reported from St. Marks Hospital in London, England [7]. The frequency of finding moderately differentiated tumors in this series (66.9%) was also similar to that reported from London [7].

It has been suggested that colorectal cancer presents at an advanced stage in the KSA and that this is a function of poor patient education and poor patient awareness of the disease [2,8]. The present series fails to support this thesis in as much as 19.7% of patients presented with adenocarcinoma confined to the organ of origin (Stage 1, Dukes stage A), 21.0% of patients presented with adenocarcinoma which had extended through the organ of origin without nodal involvement (Stage 2, Dukes stage B) and 26.9% of patients presented with nodal disease (Stage 3, Dukes stage C). In a national series from New Zealand these figures were 16.4%, 37.3% and 31.3%, respectively [3]. Similar data from the Lahey Clinic showed 22.3% of patients with Dukes A tumors, 32.9% of patients with Dukes B tumors and 20.2% of patients with Dukes stage C tumors [4].

In contradistinction to esophageal [9] cancer where "a pocket of high concentration" was observed at Qassim, there did not appear to be any regional differences in the presentation of colorectal cancer in this series.

Why Saudis should have smaller and earlier stage tumors than other Arabs is difficult to explain but it could be that non-national Arabs are too busy working in the KSA and have little time to worry about their health problems.

Why sigmoid tumors should be better differentiated and smaller and yet have a higher metastasis rate than either right-sided or rectal lesions is also difficult to explain. It is unlikely to be a sampling error due to the small group size because there were 89 patients with right-sided lesions, 61 with sigmoid lesions, and 248 with rectal tumors. Nearly 50% of sigmoid tumors had distant metastasis at the time of presentation in comparison with 24% and 25% of left-sided and rectal tumors. It could be postulated that distal early tumors would cause symptoms and result in an earlier presentation, but it is difficult to see how it could be so of right-sided lesions which traditionally are thought to present late.

Malignant colorectal neoplasia is relatively uncommon in Arabs and registry data from Kuwait suggests that the incidence rate is approximately tenth of that in the "West" [10]. Although some differences do probably exist between the disease in the KSA and the "West" (in press), it would appear from this relatively large series that in general the disease is similar to the disease that has been described in other countries. It is felt that the present series from the KFSH&RC is probably representative of the disease in Saudis at the present time in the KSA and that it may be used as a basis for further prospective studies in the future.

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ANTIBACTERIAL ACTIVITY OF FLUOROQUINOLONES LOCAL CLINICAL ISOLATES FROM A REFERRAL CENTER IN RIYADH

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جرى اختبار الحساسية لإجمالي أربع وثلاثين وألفًا من المعزولات السريرية من مركز رعاية تخصصي لستة عقاقير من مجموعة فلوروكوينولونز هي: نورفلوكساسين، وسي ١ ـ ٩٦٠. تضمنت الجراثيم التي تم اختبارها ٥٧٩ من الامعائيات، ٩٨ زائفة، ٥١ Acinetebacter ، ٥٦ مكورة معوية و ٢٥٠ عنقودية. أظهرت العقاقير الستة نشاطاً ممتازًا في المعمل مثبطة <٩٠٪ ضمن الأشريكية القولونية عند أدنى تركيز تثبيطي MIC m ٠,٠٣ ـ ٠,٥ مغ/ل، والكلبسيلة الرئوية عند ٠,١٢ ـ ٢,٠ مغ/ل، والجرثوم المعوي عند ٠,١٢ ـ ٢,٠ مغ/ل، والسراتية الذابلة عند ٠,١٢ ـ ٢,٠ مغ/ل، والزائفة الزنجارية عند ٠,٥ ـ ٢,٠ مغ/ل، والعنقودية الذهبية عند < ٠,٠٣ ـ ١,٠ مغ/ل، والعنقوديات سلبية المخثرة عند ٠,١٢ ـ ٢,٠ مغ/ل. أظهرت Xanthomonas Maltophilia شيئًا من المقاومة للنورفلوكساسين والسبروفلوكساسين واللومفلوكساسين والتيما فلوكساسين، ولكنها ثبطت بواسطة سبارفلوكساسين وسي ١ـ٩٦٠. أبدت غالبية المكورات المعوية مقاومة للنوفلوكساسين والسيبروفلوكساسين و اللومفلوكساسين وسي ١ـ٩٦٠، ولكن عقاري سبارفلوكساسين وتيما فلوكساسين تمكنا من تثبيط ٩٢٪ و ٨٢٪ من هذه المكورات على التوالي.

A total of 1,034 clinical isolates from a tertiary care center were tested against six fluoroquinolones, namely norfloxacin, ciprofloxacin, lomefloxacin, sparfloxacin, temafloxacin, and CI–960. Bacteria tested consisted of 579 strains of *Enterobacteriaceae,* 98 *pseudomonads,* 51 *Acinetebacter,* 56 enterococci and 250 isolates of staphylococci. All six fluoroquinolones showed excellent in vitro activity inhibiting >90% of *Escherichia coli* at an MIC of < 0.03–0.5 mg/L, *Klebsiella pneumoniae* at 0.12–2.0 mg/L, *Enterobacter* at 0.12–2.0 mg/L, *Serratia marcescens* at 0.12–2.0 mg/L, *Pseudomonas aeruginosa* at 0.5–2.0 mg/L, *Staphylococus aureus* at < 0.03–1.0 mg/L, and coagulase negative staphylococci at an MIC of 0.12–2.0 mg/L *Xanthomonas maltophilia* showed some resistance to norfloxacin, ciprofloxacin, lomefloxacin and temafloxacin, but was inhibited by sparfloxacin and CI–960. A majority of isolates of enterococci were resistant to norfloxacin, ciprofloxacin, lomefloxacin and CI–960, but sparfloxacin and temafloxacin inhibited 92% and 82% of these strains, respectively.

The newer fluoroquinolones are a major advance in antimicrobial chemotherapy and have evolved from chemical modifications of nalidixic acid [1]. The first breakthrough occurred during the early 1980s when norfloxacin, a second generation quinolone with 6–flourine and 7–piperazine substituents, was synthesized. The enhanced activity of this drug as an orally active agent for urinary tract infections resulted in further development of other fluoroquinolones such as ciprofloxacin and later by third generation quinolones such as lomefloxacin, sparfloxacin, temafloxacin, and CI–960 [2]. The newer 4–quinolone antibacterial agents possess a carboxyl group at position four. The addition of a piperazine at position seven confers increased antimicrobial activity, especially against P. aeruginosa. Fluorination of the nucleus at position six increases antibacterial potency. In fact, the trend in the synthesis of newer third generation agents has been to increase the number of flourine residues. Structural changes of the parent compound (Figure 1) have thus resulted in extended spectrum of activity, better penetration, and improved pharmacokinetic properties.

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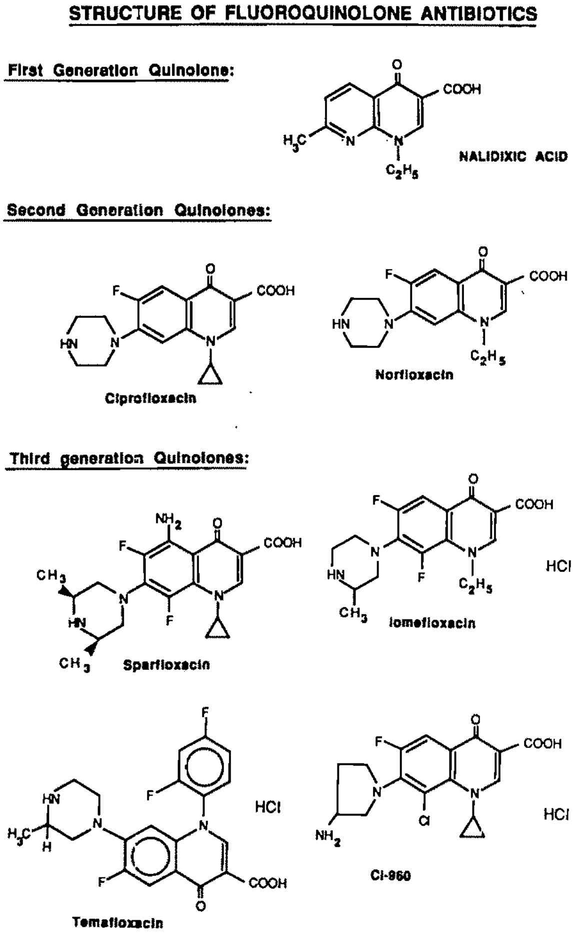
STRUCTURE OF FLUOROQUINOLONE ANTIBIOTICS
First Generation Quinolone:
NALIDIXIC ACID
Second Generation Quinolones:
Ciprofloxacin
Norfloxacin
Third generation Quinolones:
Sparfloxacin
lomefloxacin
HCl
Temafloxacin
HCl
CI-960
HCl

FIGURE 1. Chemical structure of fluorquinolones.

The newer fluoroquinolones have generated much interest because they can be administered orally as well as parenterally and are rapidly distributed in the body attaining therapeutic concentrations in most soft tissue. The fluoroquinolones have proved effective in the treatment of infections in the urinary tract, respiratory tract, soft tissue, gonnorhea, and bacterial gastroenteritis. Success has been more notable in the management of diseases caused by Gram-negative bacteria, but less so with Gram-positive infections [3,4]. In this paper we provide a comparison between in vitro activity of 6-fluoroquinolones and recently isolated bacteria in Riyadh.

Materials and Methods

A total of 1,034 bacterial strains of clinical isolates from King Faisal Specialist Hospital and Research Centre, a 550-bed tertiary care facility in Riyadh, Saudi Arabia were used for evaluation of 6-fluoroquinolones. Bacteria tested was comprised of 186 isolates of *E. coli,* 64, *K. pneumoniae,* 31 *K. oxytoca,* 62 *Enterobacter,* 24 *Citrobacter sp.,* 40 *S. Marcescens,* 38 *Proteus sp.,* 27 *Providencia/Morganella sp.,* 47 *Salmonella sp.,* 29 *Shigella sp.,* 51 *Acinetobacter sp.,* 98 *P. aeruginosa,* 31 *X. axtophilia,* 128 *S. aureus,* 122 coagulase negative staphylococci, and 56 *Enterococci.* All bacterial isolates were identified by standard procedures [5]. Antimicrobial susceptibility testing was performed by the agar dilution method as recommended by the National Committee for Clinical Laboratory Standards [6].

Throughout the study, Mueller-Hinton agar (Difco Laboratories, Detroit, MI, USA) with a pH range of 7.2 to 7.4 was used. Final concentration of drugs tested ranged between 0.03 mg/L to 32 mg/L. The inoculum consisted of 10^4 CFU per spot and prepared as described previously [6]. The Mueller-Hinton agar plates with different concentrations of fluoroquinolones were inoculated by using the Steers replicator (Craft Machine Inc., Chester, PA, USA). All organisms were incubated at 35°C for 18 to 25 hours. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29213 were used as quality control organisms. The quality control results were within expected ranges for this study. Bacteria were considered resistant when the MIC for fluoroquinolones exceeded 4.0 mg/L or as reported in the literature [6,7]. Ciprofloxacin and norfloxacin were obtained from commercial sources. Sparfloxacin and CI-960 were provided by Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI, USA), lomefloxacin by Searle Pharmaceuticals (Skokie, IL, USA) and temafloxacin by Abbott Laboratories (Abbott Park, IL, USA).

Results

One thousand thirty-four bacterial isolates comprising 579 *Enterobacteriaceae,* 98 pseudomonads, 51 *Acinetobacter,* and 306 strains of Gram-positive cocci were used to determine their MICs to norfloxacin, ciprofloxacin, lomefloxacin, sparfloxacin, temafloxacin, and CI-960 (Table 1). All the fluoroquinolones were effective against 186 isolates

TABLE 1. *In vitro Activity of fluoroquinolones against clinical isolates.*

Organism (n)*	Antibiotic	MIC mg/L			Susceptible %
		MIC_{50}	MIC_{90}	Range	
E. coli (186)	Norfloxacin	< 0.03	< 0.03	< 0.03–0.12	100
	Ciprofloxacin	< 0.03	0.12	0.03–0.5	100
	Lomefloxacin	0.25	0.5	0.12–> 32	99
	Sparfloxacin	< 0.03	0.12	> 0.03–> 4.0	99
	Temafloxacin	0.06	0.25	0.03–> 4.0	99
	CI–960	< 0.03	< 0.03	0.03–0.12	100
Klebsiella pneumoniae (64)	Norfloxacin	0.12	2.0	0.12–> 32	97
	Ciprofloxacin	< 0.03	0.25	0.06–0.25	98
	Lomefloxacin	0.25	1.0	0.25–> 32	96
	Sparfloxacin	0.06	0.5	< 0.03–> 4	98
	Temafloxacin	0.12	0.12	< 0.12–> 4	97
	CI–960	< 0.03	0.12	< 0.03–> 4	98
Klebsiella oxytoca (31)	Norfloxacin	0.25	0.5	0.25–2.0	100
	Ciprofloxacin	0.06	0.25	0.06–0.5	100
	Lomefloxacin	0.12	0.25	0.12–0.5	100
	Sparfloxacin	0.03	0.5	< 0.03–0.5	100
	Temafloxacin	0.12	0.5	< 0.06–1.0	100
	CI–960	< 0.03	0.12	< 0.03–0.12	100
Enterobacter sp. (62)	Norfloxacin	0.05	4.0	0.05–8	95
	Ciprofloxacin	0.12	2.0	0.12–4.0	100
	Lomefloxacin	0.12	4.0	0.12–> 16.0	97
	Sparfloxacin	0.03	0.12	< 0.03–1.0	100
	Temafloxacin	0.06	0.5	0.03–1.0	100
	CI–960	< 0.03	0.12	< 0.03–0.5	100
Citrobacter sp. (24)	Norfloxacin	0.25	2.0	0.12–2.0	100
	Ciprofloxacin	0.06	0.5	0.06–1.0	100
	Lomefloxacin	0.12	1.0	0.06–1.0	100
	Sparfloxacin	< 0.03	> 4.0	< 0.03–> 4.0	83
	Temafloxacin	0.5	> 4.0	< 0.03–> 4.0	83
	CI–960	< 0.03	0.52	< 0.03–0.12	100
Serratia marcescens (40)	Norfloxacin	0.5	2.0	0.25–8.0	94
	Ciprofloxacin	0.25	0.5	0.12–0.5	100
	Lomefloxacin	0.5	1.0	0.06–1.0	100
	Sparfloxacin	0.12	1.0	< 0.03–4.0	100
	Temafloxacin	0.25	1.0	0.03–4.0	100
	CI–960	< 0.03	0.12	< 0.03–0.12	100
Proteus sp. (38)	Norfloxacin	0.5	2.0	0.05–> 4.0	98
	Ciprofloxacin	0.25	0.5	0.12–1.0	100
	Lomefloxacin	0.25	0.5	0.25–1.0	100
	Sparfloxacin	0.12	1.0	0.03–4.0	100
	Temafloxacin	0.5	1.0	0.5–4.0	100
	CI–960	< 0.03	0.52	< 0.03–0.12	100
Providencia/ Morganella sp. (27)	Norfloxacin	0.25	1.0	0.25–1.0	100
	Ciprofloxacin	0.12	0.25	0.06–0.5	100
	Lomefloxacin	0.25	0.25	0.12–0.5	100
	Sparfloxacin	0.12	0.5	0.06–0.5	100
	Temafloxacin	0.25	0.5	0.12–0.5	100
	CI–960	< 0.03	0.12	< 0.03–0.12	100

TABLE 1. *Continued.*

		MIC mg/L			
Organism (n)*	Antibiotic	MIC_{50}	MIC_{90}	Range	Susceptible %
Salmonella sp. (47)	Norfloxacin	0.25	0.5	0.12–1.0	100
	Ciprofloxacin	0.06	0.25	0.06–0.5	100
	Lomefloxacin	0.06	0.25	0.06–0.5	100
	Sparfloxacin	0.06	0.12	0.03–0.12	100
	Temafloxacin	0.06	0.12	0.03–0.12	100
	CI-960	<0.03	0.03	<0.03–0.06	100
Shigella sp. (29)	Norfloxacin	0.25	1.0	0.25–1.0	100
	Ciprofloxacin	0.06	0.12	0.06–0.25	100
	Lomefloxacin	0.12	0.25	0.12–0.5	100
	Sparfloxacin	0.06	0.12	0.03–0.12	100
	Temafloxacin	0.03	0.12	0.03–0.12	100
	CI–960	<0.03	0.12	<0.03–0.12	100
Acinetobacter sp. (51)	Norfloxacin	0.5	16	0.5–>4.0	67
	Ciprofloxacin	0.25	1.0	0.25–8.0	99
	Lomefloxacin	0.5	2.0	0.50–8.0	98
	Sparfloxacin	<0.03	0.12	<0.03–0.12	100
	Temafloxacin	<0.03	0.12	<0.03–0.12	100
	CI–960	<0.03	1.0	<0.03–1.0	100
Pseudomonas aeruginosa (98)	Norfloxacin	1.0	2.0	0.5–16	95
	Ciprofloxacin	0.5	2.0	0.5–16	96
	Lomefloxacin	0.5	2.0	0.5–16	93
	Sparfloxacin	1.0	4.0	<0.03–>4.0	89
	Temafloxacin	1.0	4.0	0.06–16.0	94
	CI–960	0.12	0.5	0.12–0.5	100
Xanthomonas maltophilia (31)	Norfloxacin	2.0	16	1.0–>32	56
	Ciprofloxacin	1.0	4.0	1.0–16	92
	Lomefloxacin	2.0	16	2.0–16	85
	Sparfloxacin	0.06	0.5	0.03–1.0	100
	Temafloxacin	>8.0	>8.0	4.0–>8.0	42
	CI–960	<0.03	0.5	0.03–1.0	100
Staphylococcus aureus (123)	Norfloxacin	0.5	1.0	0.25–>2.0	100
	Ciprofloxacin	0.125	1.0	0.12–>1.0	100
	Lomefloxacin	0.25	1.0	0.12–2.0	100
	Sparfloxacin	0.12	0.5	0.12–0.5	100
	Temafloxacin	0.25	0.5	0.12–1.0	100
	CI–960	<0.03	<0.03	<0.03	100
Coagulase negative staphylococci (122)	Norfloxacin	1.0	4.0	0.5–16	94
	Ciprofloxacin	0.5	2.0	0.5–4.0	100
	Lomefloxacin	1.0	2.0	0.5–>32	92
	Sparfloxacin	0.25	4.0	0.12–8.0	97
	Temafloxacin	0.25	1.0	0.12–8.0	94
	CI–960	<0.03	0.12	<0.03	100
Enterococcus (56)	Norfloxacin	8.0	16	2.0–>32	32
	Ciprofloxacin	8.0	8.0	2.0–>32	48
	Lomefloxacin	8.0	8.0	2.0–>32	43
	Sparfloxacin	4.0	4.0	0.5–8.0	92
	Temafloxacin	1.0	8.0	0.5–8.0	82
	CI–960	8.0	8.0	1.0–8.0	36

* n = number of isolates.

of *E. coli.* Norfloxacin and CI-960 showed 90% inhibition at concentrations < 0.03 mg/L. The fluoroquionoles were 100% effective in inhibiting all tested isolates of *K. oxytoca, Providencia/Morganella sp., Salmonella sp.,* and *Shigella sp.* Norfloxacin inhibited 94% strains of *S. marcescens,* whereas ciprofloxacin, lomefloxacin, sparfloxacin, temafloxacin, and CI-960 showed 100% inhibition. The 6-fluoroquionolones showed variable inhibition to *P. aeruginosa.* Sparfloxacin was only effective against 89% of *P. aeruginosa* isolates compared to 96% for ciprofloxacin, 95% for norfloxacin, 94% for temafloxacin, and 93% for lomefloxacin. CI-960 was the most effective antibiotic inhibiting 100% of *P. aeruginosa* isolates with an MIC_{90} of 0.5 mg/L. *X. maltophilia* was relatively resistant to norfloxacin, ciprofloxacin, lomefloxacin and temafloxacin, but both sparfloxacin and CI-960 were effective.

All 128 isolates of S. aureus including 18 methicillin-resistant strains were inhibited by the fluoroquionoles with CI-960 being the most effective at concentrations of < 0.03 mg/L. Enterococci showed significant resistance to the fluoroquinolones, only sparfloxacin and temafloxacin inhibiting 92% and 82% of the isolates, respectively.

Discussion

Clinical isolates are known to be more resistant to commonly used antimicrobial agents in developing countries of Asia, Africa, and Latin America [8]. Saudi Arabia is unique in that large numbers of expatriate workers and pilgrims flock to this country annually thereby increasing the pool of resistant isolates most likely to be encountered [9]. Thus, this investigation was of particular interest because of the significantly resistant organisms used in this study against the fluoroquinolones. It has been shown previously that many Gram-negative bacteria such as *E. coli, P. mirabilis, Serratia, Enterobacter,* and *Pseudomonas* are more resistant to penicillins, cephalosporins, and aminoglycosides in Saudi Arabia than in the USA [9,10]. All the fluoroquinolones tested have been shown to be more effective against *Enterobacteriaceae* than aminoglycosides, penicillins, and cephalosporins [11].

Although all the fluoroquinolones tested showed excellent in vitro activity against most of the bacterial isolates, only two organisms, namely *X. maltophilia* and *Enterococcus,* exhibited any significant resistance. Nonetheless, sparfloxacin and CI-960 showed 100% inhibition against *X. maltophilia;* sparfloxacin and temafloxacin were also inhibitory against enterococcal isolates. Our findings are consistent with those reported in the literature [11–15].

Improved pharmacokinetic properties over nalidixic acid makes this group of antimicrobials exciting. These properties include a high permeation rate into human cells which allows access to intracellular pathogens such as *Brucella* and *Salmonella.* Some of the third generation fluoroquinolones such as sparfloxacin and lomefloxacin also exhibit increased serum levels and half-life [16,17]. For example, Morrison et al [18] reported maximum lomefloxacin serum levels of 1.11 to 7.46 mg/L for the 100 to 800 mg oral doses, respectively, and a serum half-life of approximately eight hours. Such peak levels and the half-life allows the possibility of single daily dosing as compared to twice-daily dosing for second generation antibiotics such as ciprofloxacin and norfloxacin.

All the fluoroquinolones are bactericidal and are active against bacteria whether in the rapid phase or stationary phase by exerting their action on DNA gyrase [4]. However, resistance to the fluoroquinolones has been found following therapy of infections caused by *P. aeruginosa, S. aureus,* and *B. melitensis* [3,19,20]. It remains to be seen whether widespread use will lead to a significant increase in resistance.

Many of the newer fluoroquinolones are still undergoing clinical trials, but the evidence to date suggests that this group of chemotherapeutic agents will prove to be a valuable addition in treating a wide array of human bacterial pathogens.

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BARIATRIC SURGERY IN SAUDI ARABIA

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تعتبر السمنة مشكلة صحية طارئة في المملكة العربية السعودية، حولت أعداد متزايدة من المرضى من أجل التدبير الجراحي للسمنة. أجريت عملية تصنيع طولي للمعدة لتسعة وثلاثين (٣٩) مريضًا كعلاج للسمنة المرضية. كان معدل نقص الـوزن في سنة واحدة (٣٨ مريضًا) ٣٩٪ بالنسبة للذكور و ٣٣٪ للإناث، بينما كان في أربع سنوات (٢٣ مريضًا) ٤٢٪ للمرضى من الذكور و ٤١٪ للإناث. بلغت الوفيات ٢,٥٪، وبلغت نسبة الإخفاق ١٣٪. يعتبر تصنيع المعدة الطولي علاجًا فعالاً لمرضى السمنة المرضية السعوديين طلبًا للوصول إلى ما يقارب الوزن المثالي للجسم والاحتفاظ به.

Obesity is an emerging health problem in Saudi Arabia. An increasing number of patients are being referred for surgical management of their obesity. Vertical banded gastroplasty (VBG) was performed on 39 patients as treatment for morbid obesity. The mean weight loss at one year (38 patients) was 39% in males and 33% in females. At four years (23 patients) the mean weight loss was 42% in males and 41% in female patients. The mortality rate was 2.5% while the failure rate reached 13%. Vertical banded gastroplasty is considered to be an effective treatment to achieve and sustain near ideal body weight in morbidly obese Saudi patients.

Obese patients suffer a significant handicap, both physically and socially, and are prone to potentially life threatening complications. Long-term weight control by dieting and/or other non-surgical measures often fail. Since the 1950s, a variety of surgical solutions have been sought and practiced. However, many of the procedures have been abandoned because of their serious nutritional consequences. Gastric partitioning procedure described by Mason and Ito [1] and Gomez [2] was accepted as the most optimal procedure. Nevertheless, this procedure has undergone numerous modifications [3–5]. In 1982, Mason described the vertical banded gastroplasty (VBG) which is now considered one of the operations of choice for weight reduction [6]. In this procedure, food intake is mechanically and severely restricted and sensations of satiety and distention are rapidly achieved. Attempts to continue eating promotes severe discomfort and vomiting. Such surgical treatment of morbid obesity has developed into a subspeciality known as bariatric surgery and is widely practiced in developed countries, particularly in the USA, Canada, Australia, and Scandinavia. In 1985, we had the privilege of introducing such surgery for the first time in Saudi Arabia. This report examines our experience in the management of morbid obesity in Riyadh, Saudi Arabia.

Patients and Methods

Between February 1985 and August 1989, 123 obese patients were referred to our clinic for consideration of surgical management. All were thoroughly assessed and investigated to exclude endocrine disorders. In addition, all patients underwent psychiatric assessment for suitability for surgical management. The selected patients were given a detailed and thorough explanation of the surgical procedure, its consequences, and possible complications. Each patient was interviewed by a respiratory therapist for breathing exercise instructions and given an incentive spirometer for practice at home. Food intake was limited to liquid diet for at least ten days prior to hospitalization. Hospital admission was arranged 24-hours prior to surgery. Subcutaneous heparin was com-

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menced with the premedication and continued until the fifth postoperative day. Each patient received a single dose of mefoxine 1 gm intravenously at the time of induction of anesthesia.

All patients underwent vertical banded gastroplasty performed by one surgeon (A.B.M.) as described by Mason [6]. The receiving gastric pouch was constructed to accommodate a volume of 35 to 45 mls using double applications of two rows of staples from an Auto-Suture TA 90 premium (4.8 mm staples). The pouch outlet along the lesser curve was encircled with a prolene mesh collar to prevent dilatation. Size 18 Ch nasogastric tube was positioned to transverse the pouch outlet in order to decompress the receiving gastric pouch as well as the distal stomach. By the fifth postoperative day, clear fluid intake was usually permitted. Subsequently, the patients were converted to solid food within four to six weeks. Follow-up was arranged in the Obesity Clinic 4, 8, and 12 weeks following surgery, then at three month intervals for one year and every six months thereafter.

Results

Based on our selection criteria (Table 1), only 39 patients (32%) were selected to undergo the operation of vertical banded gastroplasty. Table 2 shows the other modalities we adapted for the management of our obese patients.

All 39 patients were Saudi nationals and each was at least 100% or 55 kg overweight (based on the guidelines for body weight tables, Fogarty Center Conference on Obesity 1973). The mean age, weight, and height for each sex is shown in Table 3.

TABLE 1. *Selection criteria for vertical banded gastroplasty (VBG)*

1. At least 100% or 55 kg overweight.
2. Age between 16 and 50 years.*
3. Absence of endocrine abnormalities.
4. Absence of chronic illness and malignancies.
5. Absence of previous gastric surgery and peptic ulcer disease.
6. Satisfactory cardiac and pulmonary function.
7. Satisfactory and stable psychiatric status.
8. Failure of previous dieting/exercise regimes.
9. Saudi nationals.**

* Authors rationale.

** To ensure close follow-up of the first 50 patients for at least 3 years.

TABLE 2. *Obesity management of 123 obese patients in Riyadh.*

Type of management	No. of patients	Percentage
I. Surgical VBG	39	32%
II. Non-surgical		
Ballobes intragastric balloon	23	19%
Dental wiring	3	2%
Dieting and exercise	58	47%

TABLE 3. *Patients demography.*

	No.	%	Mean age	Mean weight	Mean height
I. Male patients	8	20	30.2	141.5	168.6
II. Female patients	31	80	27.6	124.7	156.1

All patients had perioperative true-cut needle biopsy of the liver which showed varying degrees of fatty infiltration with no other significant findings. Five patients (13%) had concomitant cholecystectomy because of gallstones and in two, appendectomy was also performed.

Perioperative Mortality and Morbidity

A 19-year-old female patient weighing 165 kg died on the sixth postoperative day from massive pulmonary embolism despite being on prophylactic subcutaneous heparin giving a mortality rate of 2.5% in this series. The remaining 38 patients tolerated the procedure well and recovery was surprisingly uneventful except in two patients. One patient developed wound infection with cellulitis and another developed severe chest infection which required mechanical ventilatory support for four days.

Follow-up

More than 45% of the patients have completed five years following surgery, while the remaining 21 patients are at least one year postoperatively. The procedure was successful in limiting solid food intake and resulting in early and rapid loss of weight in all patients. The rate of weight loss slows down and varies significantly from patient to patient following the sixth postoperative month (Table 4). The procedure was considered successful in 33 patients (85%). Figure 1 shows a com-

TABLE 4. *Mean weight loss in kilograms.*

	No. of patients	Males Mean wt.	Males S.D.	Females Mean wt.	Females S.D.	Computed + statistic	P value
Preoperative	39	141.5	9.4	124.7	18.3		
Postoperative							
at 4 weeks	38	129.4	9.9	114.2	15.6	2.85	<0.05
at 12 weeks	38	111.3	13.5	99.9	15.9	2.22	<0.05
at 36 weeks	38	94.3	9.2	88.6	14.5	1.04	NS
at 12 months	38	85.9	9.3	83.1	13.9	0.52	NS
at 18 months	36	80.5	10.4	80.5	14.5	0.02	NS
at 2 years	32	79.5	12.2	78.4	18.6	0.08	NS
at 3 years	25	82.3	5.1	76.6	20.3	0.54	NS
at 4 years	23	81.8	7.2	74.0	18.6	0.81	NS
at 5 years	17	85.9	9.3	83.1	13.9	0.52	NS

NS = Not significant

puter printout of the patients' initial weight distribution in relation to the 90th centile. Figure 2 shows the postoperative mean weight loss as it approaches the 90th centile by time. Table 5 shows the amount of weight loss in the patients

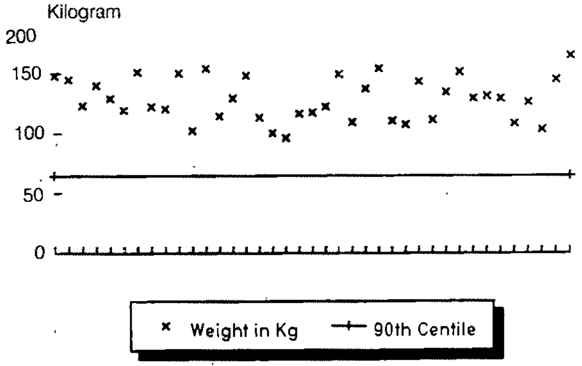

FIGURE 1. Initial weight distribution.

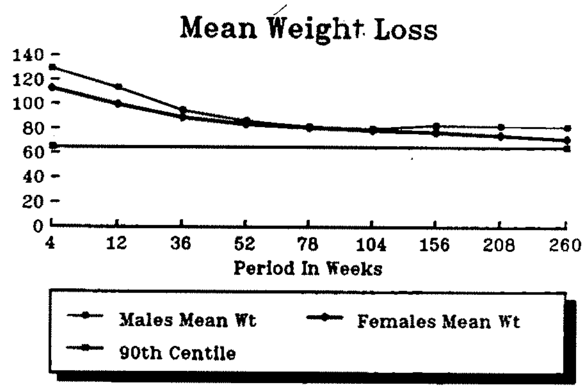

FIGURE 2. Mean weight loss in relation to 90th centile.

TABLE 5. *Amount of weight loss after two years in the first 32 patients.*

Serial number	Wt. before surgery kg	Wt. after surgery kg	Difference kg
1	148	78	70
2	145	78	67
3	123	80	43
4	140	81	59
5	129	87	42
6	165	died	–
7	119	70	49
8	151	94	57
9	122	79	43
10	120	75	45
11	150	89	61
12	102	70	32
13	154	133	21
14	114	60	54
15	129	70	59
16	148	70	78
17	113	60	53
18	117	120	+3
19	122	81	41
20	149	95	54
21	109	67	42
22	137	63	74
23	154	83	71
24	110	70	40
25	107	80	27
26	143	72	71
27	134	71	63
28	151	76	75
29	129	61	68
30	131	89	42
31	129	60	69
32	108	71	37
Mean	130.2	78.5	51.1
SD	16.1	16.1	17.5

* $P < 0.05$ * 95% CI (44.8–57.4)

who completed two years following surgery and statistical *P* value and the 95th centile. Analysis of the data showed that the weight loss is more rapid and consistent in males than in the females. Nine of the female patients underwent subsequent body contour cosmetic surgery after attaining near ideal body weight comparable to their height. Another four patients became pregnant and produced healthy normal children, but one developed an incisional hernia which required surgical repair eight months after delivery. It is worth noting that 14 patients (37%) frequently complained of dizziness and fatigue during follow-up. This was transient and resolved with reassurance and without any specific treatment as we failed to find any significant hematological or biochemical abnormalities in any of our patients.

Failures

The procedure was considered unsuccessful in five female patients (13%). Three patients disrupted the vertical staple lines opening the receiving pouch freely into the rest of the stomach with no hindrance to solid food intake resulting in rapid weight gain after an initial loss. The fourth patient developed stenosis of the pouch outlet seven months following surgery resulting in repeated vomiting, dehydration, and hypokalemia requiring repeated hospitalization. Although there was an initial good response to conservative management, the patient strongly demanded the procedure be undone. Therefore, she underwent laparotomy where only the prolene mesh collar encircling the pouch stoma was removed. Subsequently, she made an uneventful recovery but she was rapidly regaining her original weight. The fifth patient, a 21-year-old, developed depressive disorders following the breakdown of her engagement and she learned to blenderize and drink her food. Her daily oral intake was estimated between 3500 and 6000 kilo calories. When last seen nine months following surgery, she weighed 6 kg more than her preoperative weight. Subsequently, she was lost to follow-up.

Discussion

Obesity is the most common form of malnutrition in developing countries and, presently, bariatric surgery is the only effective treatment for morbid obesity. In a rapidly developing country like Saudi Arabia, obesity is emerging as a health problem affecting a large number of Saudis. The prevalence of obesity in Saudi patients attending the primary health care center of KFH at Al-Khobar was 51.5% for males and 65.4% for females [7]. This high prevalence of obesity may be attributed to the changes in the economic, cultural, and behavioral factors. Almost all patients reported here have tried many types of weight-reducing methods from articles in magazines and some joined slimming clubs and health institutes, but failed to reach and sustain ideal body weight. Since we established the Obesity Clinic at King Khalid University Hospital in 1984 and subsequently at Security Forces Hospital, an increasing number of patients are being referred for surgical management. Currently, we perform 12 to 15 gastroplasties per year. Other university hospitals in Jeddah and Dammam now perform the same procedure.

The aim of the vertical banded gastroplasty is to construct a proximal gastric compartment, measured at the time of surgery, and a non-expanding stoma to preserve the integrity of the staple lines [6,8,9]. We are implementing two modifications. One is the application of a running over and over 2/0 Vicryl suture over the staples of the gastric window, created by the premium CEEA 28, for hemostatic purposes. The second is the application of two double rows of vertical staples using two applications of Auto-Suture TA 90 or single application of TA 90B with four equidistant rows of staples.

We found the procedure relatively easy to perform. Nevertheless, it required great care in measuring the size of the receiving gastric pouch and calibrating its outlet in order to achieve good results. The preoperative assessment and the selection criteria as well as postoperative management and follow-up are equally important and contribute significantly to the success or failure of the surgical management. It is essential that the patients return as soon as possible, usually within 6 to 8 weeks, to solid food intake and not to resort to high calorie liquid food. The procedure is very effective in limiting the amount of solid food intake, even when well masticated, and hence results in a steady loss of weight. All measures should be taken to prevent the patient from taking foods that go down easily [10]. Repeated forcing of solid food and the consequent vomiting will probably contribute to disruption of the staple lines as was the case in three of our failures. From our experience, disruption of the staple lines usually occurs within six to eight months following surgery.

We have revised the procedure in one of the three failures. The revision was more difficult than the initial procedure. However, the previous application of an omental patch over the prolene mesh collar made the dissection safer and relatively easier. This patient is now nine months post-revision and is doing quite well. The second revision was performed on the woman who developed pouch outlet stenosis where we removed the prolene mesh collar during the second laparotomy. This patient requested a re-do of the procedure after her weight reached 171 kg and became severely handicapped. During the re-do surgery, we found the vertical staple lines intact but the pouch was markedly dilated. This necessitated the reconstruction of the receiving gastric pouch to a size of 65 ml and an outlet stoma calibrated to 9 mm internal diameter. Postoperative recovery was somewhat hectic and she required nursing in the surgical intensive care unit with mechanical ventilatory support for two days. She is now six months post-revision and is doing well.

Although our society is known to have a high incidence of gallstone formation [11,12], only five patients (13%) were found to have gallstones and hence have had their gallbladders removed concomitantly during the gastroplasty. Western series shows a high incidence of gallstone formation following gastric bypass or partitioning procedures [13-15].

During the follow-up period which was up to five years in 45% of the patients, none has yet developed symptoms nor shown ultrasound evidence suggesting the development of gallstones following the procedure. As well, none of our patients has developed any hemic micronutrients nor other nutritional deficiencies expected to occur with other weight reducing procedures [16-18]. It is worth noting that of the four patients who became pregnant following this procedure none complained of hyperemesis gravidarum nor required antacid medications for heartburn more commonly seen during pregnancy. The female who developed an incisional hernia became pregnant five months following gastroplasty.

Although only 45% of our patients have completed five years post-surgery, the remaining patients are doing quite well and we have no reason to anticipate additional failures. The failure rate of 13% was apparent within 12 months from the time of the surgery. Hence, we are reporting the patients who completed at least 18 months post-surgery. Therefore, we consider the success rate of 85% as a true reflection of the efficacy of the procedure.

In conclusion, we believe that there will be an increasing demand for bariatric surgery in Saudi Arabia over the next decade. Vertical banded gastroplasty offers a good choice for the management of morbidly obese patients. The morbidity and mortality rates are surprisingly low and the results are quite rewarding.

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THE SPECTRUM OF ACUTE EPSTEIN-BARR VIRUS INFECTION IN SAUDI CHILDREN

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تبقى معظم الأخماج الأولية بحمة ايشتاين - بار لدى الأطفال عديمة الأعراض. وتتفاوت السمات السريرية لدى من تظهر عليهم الأعراض. نصف في هذه الدراسة حالات ثلاثة وثلاثين مريضًا أدخلوا إلى مستشفى الأطفال بالسليمانية في الرياض بين عامي ١٤٠٩هـ - ١٤١١هـ (١٩٨٨م - ١٩٩٠م) بسبب خمج أولي حاد بحمة ايشتاين - بار. كانت معظم الظواهر السريرية الدافعة لمراجعة المستشفى التهاب السبيل التنفسي الأعلى، والحمى، واعتلال الغدد اللمفاوية، وتضخم الكبد والطحال. عانى ثلاثة مرضى من ألم المفاصل وأبدى ثلاثة مرضى مظاهر اعتلال عصبي. ظهرت لمفاويات لانطمية لدى أربعة مرضى. كان هناك ارتقاع في مستوى ناقلتي الأمين الألانينية والأسبرتية لدى قرابة ٥٤,٥٪ من المرضى.

Most of the primary infections caused by Epstein-Barr virus in children are asymptomatic. In symptomatic patients, clinical presentation is variable. We describe 33 patients admitted to Sulemania Children's Hospital, Riyadh from 1409 to 1411H (1988 to 1990G) with acute primary infection caused by Epstein-Barr virus. The clinical presentation was mostly with upper respiratory tract infection, fever, lymphadenopathy, and hepatosplenomegaly. Three patients had arthralgia and three had neurological manifestations. Only four patients had atypical lymphoctyes > 10%. Elevated serum alanine and aspartate aminotransferase levels were found in about 54.5% of the patients.

Epstein-Barr virus (EBV) has been associated with the infectious mononucleosis syndrome, Burkitt's lymphoma, nasopharyngeal carcinoma, and chronic fatigue syndrome [1]. In underdeveloped and densely populated areas of the world, 80% to 90% of children may have been infected by EBV by age five [2]. In less populated areas and among upper socioeconomic classes of developed countries, the corresponding figure is approximately 20%. Most infections during childhood are asymptomatic [3,4]. There are previous reports of EBV infection and prevalence rate of seropositivity from Saudi Arabia [5–7]. We describe 33 patients with acute primary EBV infection during childhood admitted to Sulemania Children's Hospital, Riyadh, and present clinical and laboratory findings involving these cases.

Patients and Methods

This was a retrospective analysis of records of patients admitted to Sulemania Children's Hospital in Riyadh, Saudi Arabia, from 1409 to 1411H (1988 to 1990G), with acute primary EBV infection. For inclusion in this study, the criteria included: EBV capsid antigen-IgM (EBV VCA-IgM) test positive by indirect immunofluorescent antibody test and negative EBV nuclear antigen (NA). Indirect immunofluorescent antibody test for EBV VCA-IgM and VCA-IgG was performed using EB-VCA IFA Kit II (Organon Teknika Corporation, Durham, North Carolina, USA), antibody for EBV early antigen (EA) by indirect immunofluorescence [8] and antibody to EBV nuclear antigen (NA) by anticomplement immunofluorescence (Organon Teknika Corporation, Durham, North Carolina, USA) [9].

The test for the detection of heterophil antibody was performed by monosticon slide test (Organon Teknika Corporation, Durham, North Carolina, USA).

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Results

Thirty-three patients were identified. Age distribution of these patients was; four patients younger than one year of age, 12 patients, one to two years of age, ten patients, two to four years of age, and seven patients older than four years of age. Twenty-four were Saudi (17 males). The presenting symptoms and signs are shown in Table 1. At the time of admission 18 (54.5%) patients were afebrile. No patient complained of having fatigue. Prior to admission, 12 (36.4%) patients received antibiotics. Five patients received ampicillin, three patients had maculopapular rash, and two had received ampicillin. Only one (3%) patient had a history of recurrent tonsillopharyngitis. Three patients with neurological manifestations included; facial palsy (1), encephalitis (1), and generalized convulsions (1). One patient presented with myocarditis. Two patients had generalized lymphadenopathy. No patients had eyelid edema or splenic rupture. Twelve patients were symptomatic from one to three days, and six patients had symptoms lasting more than six days. Six (18.2%) patients had radiological evidence of pneumonia. Important laboratory findings are shown in Table 2. Hemoglobin level was < 100 g/L in ten (30.3%) patients. Coomb's test was negative for all patients. Total white blood cell count ranged from 3–52 × 10^9/L. Ten (30.3%) patients had lymphocytes < 50%. Platelet count was > 100 × 10^9/L for all except one patient who had a platelet count of 5 × 10^9/L. The range for absolute lymphocyte count was 1,368 to 28,638, and for absolute atypical lymphocytes, zero to 4,255. Only four patients had atypical lymphocytes 10% or greater. Alanine aminotransferase was > 40 U/L in 18 (54.5%) patients and aspartate aminotransferase was > 40 U/L in 12 patients. Heterophile antibody test was positive in eight patients. Age distribution of these patients included; three patients less than six months of age, three patients between 12 to 24 months of age, and two patients > 24 months. Table 3 notes the results of serological tests for EBV markers. Hepatitis B surface antigen (HBsAg) was positive in one patient. Hepatitis A virus (HAV) IgM was positive in one patient.

TABLE 1. *Symptoms and signs.*

	No.	Percent
SYMPTOMS		
URTI symptoms	20	60.6
Fever (temperature > 38°C)	15	45.5
Vomiting	10	30.3
Abdominal pain	5	15.2
Neurological symptoms	3	9.1
Arthralgia	3	9.1
Jaundice	2	6.1
SIGNS		
Hepatomegaly	19	57.5
Cervical lymphadenopathy	12	36.4
Splenomegaly	11	33.3
Otitis media	11	33.3
Pharyngeal exudate	7	21.2
Skin rash	3	9.1

URTI = upper respiratory tract infection.

TABLE 2. *Laboratory findings.*

Test	Mean + SD
Hemoglobin (g/L)	100 ± 10
Total WBC (× 10^9/L)	13.4 ± 9.0
Lymphocytes (absolute no.)	7204 ± 6290
Atypical lymphocytes (absolute no.)	739 ± 1144
Alanine aminotransferase (U/L)	205 ± 451
Aspartate aminotransferase (U/L)	221 ± 483

Mean + SD = mean + standard deviation; WBC = white blood cells.

TABLE 3. *EBV serology.*

Test	No. positive	Percent
EA	10	30.3
VCA IgM	33	100
VCA IgG	15	45.4
NA	0	0

EA = early antigen; VCA IgG = viral capsid antigen immunoglobulin G; VCA IgM = viral capsid antigen specific immunoglobulin M; NA = nuclear antigen.

Discussion

Primary acute Epstein-Barr infection is usually asymptomatic in young children. In symptomatic patients the manifestations are variable.

Three patients presented with maculopapular rash. Two (66.6%) had received ampicillin prior to the onset of rash. Skin rash is seen in approximately 3% to 15% of patients with infectious mononucleosis. After receiving ampicillin, a rash may be observed in up to 80% of patients with infectious mononucleosis [10]. Among the many different manifestations of EBV infections, neurological disturbances are less frequently observed, but they are diverse in nature. Bell's palsy, aseptic meningitis, and coma have been reported in the literature [11]. Our series included three patients; one with Bell's palsy, one with encephalitis, and one with generalized convulsions. Splenic rupture is the most feared complication of infectious mononucleosis. Fortunately, none of our patients presented with splenic rupture.

Atypical lymphocytes are usually > 10 in patients with acute infectious mononucleosis. In our series, only four (12.1%) patients had atypical lymphocytes 10% or more. Heterophile antibody test is usually negative in younger children [12]. In our series, only eight (24.2%) patients had positive heterophile antibody test. Three were younger than 12-months-old. In an earlier report from Saudi Arabia, Hossain reported 11 children with infectious mononucleosis caused by EBV [6]. Six were heterophile positive. All children in this study were 5 to 15-years-of-age. In contrast, in our study, all patients with positive heterophile test were five-years-of-age or younger. HAV IgM was positive in one patient. This may be due to the coincident acute hepatitis A virus infection. HBsAg was positive in one patient. This may also be due to the carrier status of the patient since other markers of hepatitis B virus were absent.

In summary, acute primary infectious mononucleosis may present with a wide variety of symptoms and signs in children. Atypical lymphocytes are not always increased and heterophile antibody test is positive in only a small percentage of patients. Specific EBV markers for the diagnosis of acute Epstein-Barr virus infection may be the only way of confirming the diagnosis of acute EBV infection in children.

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NEURAL TUBE DEFECTS IN SOUTHWESTERN REGION OF SAUDI ARABIA

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كان معدل وقوع عيوب تخلق الأنبوب تالعصبي في منطقة عسير، في جنوب غربي المملكة، بين شهري ديسمبر ١٩٨٩م وديسمبر ١٩٩٠م، ٠,٨٢ / ١٠٠٠. استخلصت هذه النتائج من مسح أجري على جميع حالات عيوب تخلق الأنبوب العصبي التي أحيلت إلى مستشفى عسير المركزي بأبها. شوهد غياب الدماغ لدى ٠,٤٣ / ١٠٠٠ مولود، والسنسنة المشقوقة المتكسية في ٠,٣٣ / ١٠٠٠. والقيلة الدماغية في ٠,٠٨ / ١٠٠٠. جاءت النتائج الوحيدة التي يمكن مقارنتها بنتائجنا من المملكة في تقرير ثليجي ومساعديه من المنطقة الشرقية في عام ١٩٨٦م حيث وجد أن المعدل الإجمالي لعيوب تخلق الأنبوب العصبي يبلغ ١,٦ / ١٠٠٠ موزعة على النحو التالي: غياب الدماغ ١ / ١٠٠٠، والسنسنة المشقوقة ٠,٣٣ / ١٠٠٠، والقيلة الدماغية ٠,٢٩ / ١٠٠٠. تبين أن المعدل الإجمالي لوقوع عيوب تخلق الأنبوب العصبي، غيبة الدماغ والقيلة الدماغية، حسب المسح الذي أجريناه، أقل بدرجة هامة (٠,٠٥ ∇n°) بينما ظل معدل وقوع السنسنة المشقوقة كما هو (٠,٠٥ ∇m°).

During December 1987 to December 1990 the incidence of neural tube defects in the Asir region located in southwestern Saudi Arabia was 0.82/1000. These results were drawn from a survey conducted of all cases of neural tube defects referred to the main hospital at Abha City (Asir Central Hospital) (ACH). Anencephaly was seen in 0.43/1000 births, spina bifida cystica 0.33/1000, and encephalocele 0.08/1000 births. The only comparable results to ours from Saudi Arabia were reported in 1986 by Thaliji et al [7] from the eastern province who found the overall incidence of neural tube defects to be 1.6/1000, anencephaly 1/1000, spina bifida 0.33/1000, and encephalocele 0.29/1000. The overall incidence of neural tube defects, anencephaly and encephalocele found in our survey was significantly lower ($P < 0.05$) while the incidence of spina bifida remained the same ($P > 0.05$).

The incidence of neural tube defects has long been recognized to vary widely according to geographical distribution, ethnic background, maternal and various socioeconomic factors [1]. Environmental factors such as diet and vitamins have also been incriminated [2–4]. There are several reports on the incidence of these defects in the Middle East including Saudi Arabia [5–8]. The incidence of neural tube defects is showing a steady and significant decrease throughout the world including many parts of the Middle East [5,9,10]. This is largely attributed to the improving socioeconomic conditions in the Middle East [7]. In societies where abortion is permitted, the incidence of liveborn neural tube defects has been greatly reduced by antenatal screening and termination of pregnancy [11–13].

This paper is an assessment of the current rates of neural tube defects in the southwestern region of Saudi Arabia.

Materials and Methods

Asir Central Hospital (ACH) is the referring hospital for all cases of spina bifida cystica and encephalocele from the whole of the Asir Province located in the southwestern region of Saudi Arabia. The topography of this region represents two varying geographical zones: 1) the highland which consists of a chain of the Sarwat mountains running parallel to the Red Sea with an altitude varying between 8,000 to 10,000 feet above sea level. The weather is cool and the average annual

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rainfall ranges from 200 to 300 mm; and 2) the lowland consists of desert and a few valleys where the weather is very hot and dry yearlong.

During December 1987 to December 1990, a total of 74,923 births took place in the region. Medically supervised deliveries represented two-thirds of all. A total of 49,280 births (65.8%) took place in hospitals while the rest remained at home with very few admitted to the primary health care centers.

The records of spina bifida cystica and encephalocele cases referred to Asir Central Hospital were reviewed with most patients being referred from distant areas with no accompanying relatives. The information provided with regard to socioeconomic, antenatal, mode of delivery, and immediate neonatal period was inadequate. Cases of anencephaly were extrapolated from hospital records in the region. No information regarding anencephalic cases born at home were discovered.

Definitions

1. Spina bifida cystica includes the following conditions: meningomyelocele and meningocele. Meningomyelocele is a midline defect of the skin, vertebral arches and neural tube. It is a skin defect covering the back with its borders found laterally by the unfused neural arches of the vertebrae which in most cases is covered by a transparent membrane where CSF may accumulate leading to the formation of a sac. Meningocele is herniation of the meninges and the defect is covered by normal skin.
2. Encephalocele is defined as herniation of the brain through a defect in the skull.
3. Anencephaly is defined as the absence of the membranous skull and the cerebral hemispheres.
4. Neural tube defect is the term used to define the above conditions collectively.

Statistical Analysis

Chi-square test is used for statistical analysis.

Results

During the study period, 52 cases of neural tube defects were encountered (0.82/1000 births); 25 (0.33/1000) were spina bifida cystica, six (0.08/1000) encephaloceles, and 21 (0.43/1000) anencephaly (calculated from among hospital deliveries only). Twenty-six cases were referred from each of the highland and lowland areas. The overall male to female ratio was 0.71:1. In cases of spina bifida, the ratio was 0.92:1, 1:1 for encephalocele and 0.5:1 for anencephaly (Table 1). Spina bifida cystica cases comprised 22 cases (88%) of myelomeningocele, and three (12%) cases of meningocele. The sites of the lesions were cervical (4), dorsolumbar (13), lumbar (1), lumbosacral (5), and sacral (2). This indicates that lumbar involvement was indicated in 72% of our cases (Table 2). Hydrocephalus was detected in 23 of the cases (risk factor 92%). Orthopedic problems such as dislocated hips, varus and valgus deformities of the feet were a universal feature in cases of myelomeningocele where the dorsal and lumbar regions were involved.

Five (83.3%) cases of the encephaloceles were occipital while only one (16.7%) was frontonasal (Table 3). Five cases of encephalocele had other associated malformations (a risk factor of 83%). Malformations encountered were: microcephaly (2) constituting the Meckel Gruber syndrome. Others noted were: facial defects/coloboma/phocomelia (1), vertebral anomalies (1) and agenesis of the corpus callosum (1) (Table 4).

Three cases of spina bifida referred demonstrated other major malformations (a risk factor of 12%). One baby had polycystic kidneys, another baby had lumbar teratoma with vertebral anomalies, and the third was an infant born to a diabetic mother. This infant also had hypertrophy of the interventricular septum (Table 4).

TABLE 1. *Neural tube defects in southern Saudi Arabia, December 1987–December 1990.*

Neural tube defects	No. (%)	Incidence	Male to Female Ratio
Spina bifida	25 (48.1)	0.33/1000	0.92:1
Myelomeningocele 22 (88%)			
Meningocele 3 (12%)			
Encephalocele	6 (11.5)	0.08/1000	1:1
Anencephaly	21 (40.4)	0.43/1000	0.5:1

TABLE 2. *Spina bifida — site of lesion.*

Level	No. of patients (%)
Cervical	4 (16)
Dorsolumbar	13 (52)
Lumbar	1 (4)
Lumbosacral	5 (20)
Sacral	2 (8)
Total	25 (100)

TABLE 3. *Encephalocele — site of lesion.*

Level	No. of patients (%)
Occipital	5 (83.3)
Frontal	1 (16.7)
Total	6 (100)

TABLE 4. *Neural tube defects (NTDs) — associated anomalies.*

NTD (Total No.) No. affected (%)	Anomaly	No. of cases
Encephalocele (6) 5 (83%)	Meckel Gruber syndrome	2
	Facial clefts/coloboma/ phocomelia	1
	Vertebral anomalies	1
	Agenesis of corpus collosum	1
Myelomeningocele (25) 3 (12%)	Polycystic kidneys	1
	Lumbar teratoma/vertebral anomalies	1
	Infant of diabetic mother/ hypertrophic interventricular septum	1

Discussion

There are only a few reports on the incidence of neural tube defects from Saudi Arabia [6,7]. In our survey we estimated the incidence of neural tube defects in the southwestern region of Saudi Arabia. The recognition of the incidence of these defects and its trend over the years may be very important and useful in the planning and evaluating of health care programs [11]. Our data on spina bifida and encephalocele represents an approximate true population rate for this region because babies whether delivered in-hospital or at home, were referred to Asir Central Hospital. However, the incidence of anencephaly only represents the rate among hospital deliveries. The only literature from this region was reported in 1985 by Maclean [6] who noted the incidence of spina bifida to be 1.1/1000 [6]. Maclean's figures were not statistically significant because his study only involved a very small selected population (deliveries at Khamis Mushayt Military Hospital). Maclean suggested that there might be a difference in the incidence according to rainfall and other climatic variations by comparing the data from Khamis Mushayt Military Hospital to the data from Tabouk Military Hospital [6]. To date we have not found any difference in the incidence between the highlands (26 cases) and the lowlands (26 cases) of this region. In 1986, Thaliji et al [7] found the incidence of spina bifida to be 0.33/1000 births, encephalocele 0.29/1000, and anencephaly 1/1000 [7] in the eastern province of Saudi Arabia. Our survey indicated the incidence of spina bifida to be the same as Thaliji et al [7] ($P > 0.05$) but we encountered a significantly lower incidence of anencephaly ($P < 0.05$) and a much lower incidence of encephalocele ($P < 0.05$). In 1984, Al-Awadi et al found the incidence of anencephaly in Kuwait to be 1.33/1000 [5]. Our corresponding incidence was 0.43/1000 which is significantly lower ($P < 0.05$). In 1988, Aljawad et al from Abu Dhabi found the combined incidence for both spina bifida and encephalocele to be 0.54/1000 [8]. Our corresponding incidence of 0.43/1000 was also lower.

More recently, a dramatic decline in the incidence of neural tube defects has been noted in many parts of the world. This decrease is not only due to antenatal diagnosis and termination but also indicates a significant decrease in the overall incidence [10–13]. In 1982, Windham and Edmonds investigated the decline in the incidence of neural tube defects in the USA. They obtained the data from various sources. They found the decrease in the annual rate to vary from 3.1% to 7.1%. This decrease was noted in all variables: race, sex, and birth status for each defect. The decrease was higher among stillbirths than among liveborn infants [11]. The data from England and Wales around this time showed an average annual decrease of 10.6% in the incidence of neural tube defects (office of Population Census and Surveys Monitor, 1981). In 1984, Carstairs and Cole found a true decrease in the incidence of neural tube defects while taking into consideration the termination of pregnancy following alpha fetoprotein screening [13].

We have noted female predominance in the rates of myelomeningocele and anencephaly which seems to be a universal feature [14], whereas encephalocele occurred at equal frequencies in both sexes. The site of the lesion in spina bifida cystica cases was predominantly located in the dorsolumbar region and that of encepaloceles was located in the occipital region (Table 3). This follows the western trend in the distribution of these lesions [15]. We have noted that 26% of the spina bifida cystica and encephalocele cases were associated with other major congenital malformations. The risk factor was 12% for spina bifida cystica and 83% for encephalocele. Table 4 shows the predominance of other cranial anamolies in encephalocele cases. Only one baby (myelomeningocele case) was detected by initial examination to have gross renal anomaly (polycystic kidneys) (Table 4). In 1987, Whitaker and Hunt found 17 renal anomalies in 190 patients with neural tube defects [16]. The interesting finding in their study was the correlation between the spinal defect level and the renal anomaly. In over one-half of the cases involved, the renal anomaly was ureteral duplication. Therefore, it seems detailed screening is likely to reveal more renal anomalies.

Thaliji et al from the eastern province of Saudi Arabia found that 15% of all cases of neural tube defects were associated with other congenital defects [17]. In 1982, Khoury et al found this incidence to be 12% from the Center for Disease Control (CDC) nationwide and 20% from the Atlanta Surveillance Systems [17]. It is difficult to compare our results with these studies as we have no records of the associated congenital anomalies in cases of anencephaly. However, our finding of a 12% incidence of associated congenital malformations in cases of spina bifida cystica is consistent with the international rate for this association.

In conclusion, we hope our study will be a useful reference for future clinicians who will assess the incidence of neural tube defects in this region and other parts of Saudi Arabia.

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THE PREVALENCE OF HIRSUTISM IN IRAQI FEMALES

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جمعنا عينة عشوائية قوامها ٣٢٥ امرأة ودرسناها لتقصي وجود الزبب. تراوحت الأعمار من ١٦ إلى ٤٥ سنة، وبلغ متوسطها ٢٧,٧ ± ٧;٤ ام. وطبقًا لطريقة ماكنايت [٢] كان يوجد زبب لدى ٥٩٪ من الإناث في مناطق مختلفة، منفردة أو متعددة، وكانت أعمار الغالبية منهن، وفقًا لنظام فيريمان - غالويه [٤]، تتراوح بين ٢٠ و ٣٤ سنة. كانت نسب وقوع الأمراض المرافقة مثل الكلف والعُدّ الشائع والحاصة من النمط الأنثوي لا تختلف كثيرًا في العينة الإجمالية عما هي عليه في مجموعة الزبب.

A random total of 325 females was collected and studied for the presence of hirsutism. Ages ranged from 16 to 45 years with a mean 27.7 ± 7.4 SD. According to the Mcknight method [2], 59% of females had hirsutism in different areas, single or in combination and most, according to the Ferriman-Gallwey [4], scoring system were 20 to 34 years of age. The incidence of associated diseases such as melasma, acne vulgaris, and female pattern alopecia were not much different in the total females and in the hirsute group studied.

Hirsutism is the growth of terminal coarse pigmented hair covering an androgen sensitive area of the body [1]. Various sites are involved in different patients and races [2]. It is generally agreed that dark haired, dark pigmented whites of either sex tend to be more hirsute than blonde or fair-skinned persons [3]. Abnormal hair distribution seems to be a common problem among Iraqi females. This abnormal pattern of hair growth usually raises the suspicion of endocrine dysfunction and constitutes one indication for specialized investigations of the patient. To establish a baseline for the selection and treatment of such cases, it is important to understand and study about the hair distribution in the general population of Iraqi women.

The aim of this study was planned with these considerations in mind.

Results

A total 325 females were seen and ages ranged from 16 to 45 years with a mean of 27.4 ± 7.4 SD, while the age of females with hirsutism ranged from 16 to 45 years with a mean of 26.6 ± 6.4 SD. Family history of hirsutism was observed in 48.4% (93 females) of the hirsute women. No females with hirsutism had any endocrinological problems.

The results of hair distribution assessment were recorded according to the Ferriman-Gallwey scoring system [4] and according to the Mcknight method (Table 1). In the latter method it was found that 59% (192 of 325) of the females assessed had hirsutism.

The associated abnormalities and diseases in females with hirsutism are shown in Table 2. There was little difference in the incidence of these problems in total females assessed and in hirsute women.

Patients and Methods

A total of 325 females were seen at random between November 1988 to January 1989. The source of females chosen were mainly from medical schools and offices and ages ranged from 16 to

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45 years with mean of 27.4 years.

In all patients assessed, a complete history was taken especially regarding marital status, history of drug intake such as steroids and psoralen compounds, local inflammation or trauma. In addition, any history of hirsutism in the patients and their families, menstrual cycles, gynecological diseases and any associated disorders were recorded. A full examination was performed to assess body hair distribution and other associated medical problems. The two methods used for the assessment of hair distribution were Mcknight [2] and Ferriman-Gallwey [4].

According to Mcknight [2], the body was divided into the following regions: face (upper lip, chin, and the sides of the face), neck, shoulders, chest (circumareolar and central area), upper and lower back, upper and lower abdomen, and limbs. The female was considered to be hirsute when she had coarse terminal hair of 0.5 cm minimal length on any of these areas [2], absence of terminal hair or the presence of few hairs, widely-spaced, considered as non-hirsute. Ferriman-Gallweys' [4] method of hair assessment was applied in this study.

TABLE 1. *Hirsutism in different body sites according to Mcknight's method of hair distribution assessment.*

Body sites	No. of females	Percent of 192	Percent of 325
Face			
Upper lip	26	13.5	8.0
Chin	59	30.7	18.1
Upper lip and chin	10	5.2	3.0
Sides of face	29	15.1	8.9
Upper lip chin sides of face	10	5.2	3.0
Neck	30	15.6	9.2
Chest			
Circumareolar	109	56.8	33.5
Central	19	9.9	5.8
Combined	13	6.8	4.0
Abdomen			
Upper abdomen	24	12.5	7.4
Lower abdomen	43	22.4	13.2
Male pubic pattern	10	5.2	3.0
Shoulders	4	2.0	1.2
Back			
Upper back	9	4.7	2.7
Lower back	27	14.1	8.3
Limbs	54	28.1	16.6

TABLE 2. *Associated disorders in randomly selected females and in hirsute women.*

Associated disorders	Hirsute cases 192	Percent of 192 hirsute women	No. of cases in 325	Percent of 325
Irregular cyle	31	16.1	50	15.4
Female pattern alopecia	7	3.6	12	3.7
Acne vulgaris	50	26.0	72	22.2
Melasma	42	21.9	69	21.2
Galactorrhea	1	0.5	1	0.3

Discussion

Hirsutism is a common problem and in most instances is associated with increased androgen production [3]. There are many etiological factors involved in the pathogenesis of the disease but the most common are polycystic ovarian syndrome and idiopathic hirsutism, but this is rarely associated with endocrine disease [5]. Racial and hereditary factors are important. Previous inquiries conducted among groups of English, American, Swedish, and Indian women suggest considerable variety of hair distribution in different racial types examined [2]. It is generally accepted that women of Mediterranean or Southern European countries have more coarse hair while those from Asian countries have much less hair [5].

Many studies were performed on hirsutism in Iraqi females but all were concerned with the etiology and pathogenesis of the disease [6]. In order to establish a baseline for the selection and treatment of such patients, the present study was carried out to determine the prevalence of hirsutism in Iraqi females who did not complain of virilizing or other endocrine disorders.

The present survey demonstrated that the prevalence of hirsutism according to Mcknight was 59% of the females; the face was affected in 26.8% which is comparable to the Welsh study (26%) [2] but more on the chin than on the upper lip. Chest hirsutism mainly around the nipples of breasts or on the central part of the chest was found in 36% which was much higher than the Welsh study (17%) [2]. On the contrary, Iraqi females have less abdominal coarse hair mainly on the linea alba (20.8%) compared to people of Welsh origin (35%).

When we compared the present study with Ferriman-Gallweys' work we found that hirsute women with grades 3 and 4 were much more commonly present.

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CT SCAN FINDINGS OF OCCULT SINUS PATHOLOGY IN ASYMPTOMATIC INDIVIDUALS

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أجرينا ١١٤ مسحًا طبقيًا على الجمجمة بالكمبيوتر لتقصي المراضه الخافية في الجيوب لدى من لا يشكون من أية أعراض. كما أجرى التصوير التصوير الطبقي استقصاء لمناطق أخرى في الجمجمة. لم يكن لدى أي من المرضى أعراض تتعلق بالأنف أو الجيوب. وجدت مراضة خافية في الجيوب الغربالية في ما نسبته ٢٩٪ وكانت على شكل انتفاخ في الغشاء المخاطي. توزع حدوث المراضة الخافية كما يلي ١٤٪ في الجيوب الفكية، و ٤,٨٪ في الجيوب الجبهية، و ٤,٦٪ في الجيوب الوتدية. ولما كانت الجيوب الغربالية معرضة لأكبر نسبة من احتمال الاصابة بالمراضة الخفية فانه لا ينبغي اعتبار ظهور تغيم في الجيوب الغربالية في صور المسح الطبقي بالكمبيوتر مسؤولاً عن أعراض يشكو منها المريض وبخاصة حين استقصاء حالات الصداع.

One hundred-fourteen computed tomographic (CT) scans of the skull region were revised for occult sinus pathology in asymptomatic individuals. The scans were conducted to investigate other skull regions. None of the patients had nasal or sinus symptoms. Twenty-nine percent of the ethmoid sinuses had occult pathology mostly in the form of thickened mucous membrane. Occult pathology occurred in 14% of maxillary sinuses, 4.8% of the frontal sinuses, and 4.6% of the sphenoid sinuses. As ethmoids carry a high incidence for possible occult pathology, isolated clouding of the ethmoids in CT scans should not be regarded as a cause for patients' symptoms especially in headache investigation.

Inflammatory and allergic changes of the paranasal sinuses can usually be demonstrated radiologically. These are usually in the form of mucosal thickening, air fluid level, or total sinus opacification. In chronic cases of sinusitis it is possible to have thickened sclerotic sinus walls [1].

However, conventional radiography showed that between 15% and 26% of asymptomatic individuals have abnormal x-ray findings of probable inflammatory or allergic origin [2,3].

Also, mucocele of the maxillary sinus is not a rare incidental radiological finding. It is present in almost 10% of cases [4].

Again, in some cases, plain radiography failed to grasp gross pathology in the paranasal sinuses. Watt-Boolsen and Karle (1977) [5], and Pfleiderer et al (1984) [6], discovered fluid in the antral puncture in 24% and 9%, respectively of radiologically normal sinuses, but clinically suspected to have sinusitis.

Computed tomography (CT) is now the best measure for imaging the sinuses [7], and clinically significant ethmoid disease may be present with relatively minimal plain radiological findings that would be quite evident on CT scan [8–10].

In this work, CT scans of paranasal sinuses were studied for possible occult pathology in asymptomatic individuals.

Material and Methods

One hundred fourteen CT scans of the skull region were studied. None of the scans was conducted to investigate the paranasal sinuses specifically, but were to study the orbit, sella turcia, facial bones, or parotid region.

Some of the paranasal sinuses came to appear incidentally in some of the cuts. The age range of patients was between 18 and 61 years, with a mean

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age of 36 years. Fifty-four percent of the patients were males.

The CT scans were reviewed by the author retrospectively to locate any benign occult pathology, namely sinus opacification, thickened mucous membrane, or the presence of polypi or cysts.

Some of the scans included both axial and coronal cuts. In others, only one cut was available.

CT scans of patients who had nasal or sinus symptoms documented in their files were excluded. Only scans of patients who were asymptomatic were included in this study.

Results

Results of the 114 CT scans studied are shown in Table 1. The ethmoid sinuses were most commonly seen in approximately 89% of the cases. Pathological changes were present in 29% of the ethmoid sinus scans. The sphenoid sinus was shown in 76% of the scans but pathological changes occurred in only 4.6% of the scans. The least seen sinus in the scan was the maxillary sinus as it appeared in only 31% of the cases and pathological changes occurred in 14% of these scans. Figure 1 shows the incidence of occult pathology in each sinus seen in the CT scans.

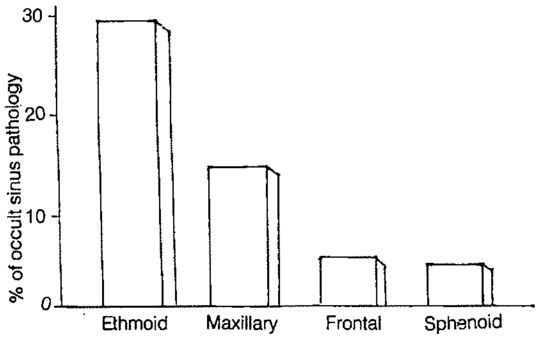

FIGURE 1. Incidence of occult sinus pathology in asymptomatic individuals in different sinuses.

Discussion

Occult sinus pathology was found in 15% to 26% of plain radiography of paranasal sinuses in asymptomatic individuals [2,3]. Several explanations have been reported [11]. First, sinusitis may be more common than is generally believed. Second, patients may demonstrate abnormalities on x-ray film long after acute inflammation has subsided. Third, some phases of sinusitis may not produce symptoms. Also, sinus films of asymptomatic individuals who travel at high altitudes or in poorly pressurized aircrafts often show abnormalities [11]. The most likely explanation is that these changes represent residuum of previous inflammation rather than active disease. This is particularly true for ethmoid sinuses [12]. In this study, ethmoid sinuses (seen in 89% of the scans) were the most commonly demonstrated. This is because most of the scans studied were directed at the orbit or sella turcia region. Again, ethmoids had the highest incidence of occult pathology, found in 29% of cases. This figure was 14% for the maxillary sinus and was as low as 4.6% for the sphenoid. The complex anatomy of the ethmoid sinuses and the fact that they can be compromised easily and would require a longer time for complete resolution, may explain the large discrepancy in the incidence of occult pathology. Also, the higher incidence of occult ethmoid pathology than previously reported with plain radiography is a reflection of the higher sensitivity of CT scan.

Cysts of the maxillary sinus were seen in 8.5% of asymptomatic individuals. This figure is closely related to the 10% previously reported by Sofferman (1977) [4].

Radiological diagnosis of nasal polyposis is less sensitive than clinical diagnosis as many of clinically detected very small polypi go undetected on plain film and CT scan [8]. This explains the

TABLE 1. *Number of sinus scans studied and number of sinuses showing occult pathology.*

Sinus studied	No. of CT scans showing sinuses	% of CT scans showing sinuses	% of scans evident pathology	No. of scans evident pathology	No. of scans w/complete opacification	No. of scans w/thickened mucous membrane	Other pathology
Ethmoids	102	89	29	30	4	26	–
Maxillary	36	31	14	5	–	3	2 (cyst)
Frontals	44	37	4.5	2	–	2	–
Sphenoid	86	76	4.6	4	–	4	–

absence of any polypi in the CT scans in the study.

In conclusion, it is evident that ethmoid sinuses carry a high incidence of possible occult pathology. This suggests that isolated clouding of the ethmoids demonstrated in CT scans is unlikely to cause symptoms in such patients, but it is likely to do so if associated with symptomatic sinusitis or when other sinuses are also involved. This is of great importance, particularly when investigating the causes of headache by CT scans of the skull and sinuses.

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A STUDY ON DIARRHEAL DISEASES IN CHILDREN UNDER FIVE YEARS OF AGE

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أجريت دراسة مقطعية على داء الإسهال لدى الأطفال دون سن الخامسة بإجراء مسح استقصائي من منزل إلى آخر في المنطقة الشرقية بالمملكة العربية السعودية. كان الهدف الأساسي من الدراسة هو تحديد المراضة بداء الإسهال وعلاقتها بمختلف المتغيرات وأساليب التدبير المتبعة خلال نوبة الإسهال. شملت جمهرة الدراسة ١١٠٥ أسرة لديهم ما مجموعه ٢٠٠٥ طفلاً تقل أعمارهم عن خمس سنوات تم اختيارهم من مجمل المنطقة الشرقية. لوحظ أن نسبة الانتشار كانت تعادل ٦,٧٪ خلال فترة أسبوعين مما يعني أن معدل الإصابة السنوية يعادل إصابتين لكل طفل سنويًا. كان معدل انتشار الإسهال مترابطاً بدرجة كبيرة بالعمر وطريقة حفظ المياه وأنماط التغذية، في حين أنه كان أقل انتشاراً بين الأطفال الذين يرضعون حليب الأم. عولجت غالبية حالات الإسهال في المراكز الصحية حيث أعطيت العقاقير لنسبة ٢٧٪ منهم فقط. أعطي محلول يحتوي على سكر وملح علاوة على السوائل المنزلية لما نسبته ٤,٤٦٪ في حين تلقى ٢٣٪ المحلول الخاص بعلاج التجفاف (ORS)

A cross sectional house-to-house survey on diarrheal disease in children less than five-years-of-age was conducted in the Eastern Province of Saudi Arabia. The main objective was to determine diarrheal disease morbidity and its relationship with different variable factors and management practices during the episode of diarrhea. The survey population included 1,105 households with 2,005 children under five-years- of-age selected from the entire Eastern Province. The prevalence observed was 7.6% during a two-week period giving an annual incidence of two episodes per child per year. Diarrheal morbidity was significantly associated with age, water storage, and feeding patterns. Diarrhea morbidity was less prevalent among children receiving breast milk. The majority of cases with diarrhea were treated in health facilities where 27% were given drugs only. A solution containing sugar and salt in addition to home fluids were given to 46.4% while 23% received oral rehydration solution (ORS).

Diarrhea associated morbidity and mortality in children under five-years-of-age is a major health problem in all developing countries. Health planning for diarrheal disease must be in response to both epidemiological patterns and local perceptions of the health and illness [1]. Although mortality associated with diarrhea is less in some countries, its morbidity imposes a heavy burden on health services. The disease is predominantly pediatric and can have a detrimental effect on nutritional status, growth, and general health of children [2,3].

To obtain baseline information, a community based house-to-house survey was planned and conducted in the Eastern Province during the month of November 1988G (Jumada Awal 1409H). The objectives of the survey were: 1. To obtain information on diarrhea morbidity and its prevalence in children under five-years-of-age from a multi-stage cluster random sampling method; 2. To correlate diarrhea morbidity with different variable factors and feeding practices; and 3. To assess treatment practices and the use of oral rehydration therapy, especially oral rehydration solution (ORS) during diarrheal episodes.

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Material and Methods

This survey of morbidity due to diarrheal disease was conducted in the population of Eastern Province, Saudi Arabia. For the estimation of sample size and procedure of sampling, a multistage cluster sampling method was used as recommended by the World Health Organization in 1986 [4]. Subjects of the study were children younger than five-years-of-age and a sample unit included a cluster containing 40 households. The methodology used was the selection of a starting household for a cluster and the head of the family/housewife or a responsible member of the family was interviewed.

A predesigned and pretested questionnaire was used to collect information on age, sex, nationality, mother's education, occupation of the head of the family, housing, sanitation, water supply, feeding, and treatment practices during a diarrhea episode. The survey period for the purpose of data collection was the two-week period preceding the interview. Children who had diarrhea during this period (including the day of survey) were included. Diarrhea was defined as the passage of three or more stools per day with change in consistency. Bivariate analysis using the Chi-square test was applied to data to test the significance of difference in diarrheal morbidity and different variables [5].

Results

A total of 2,005 children younger than five-years-of-age were surveyed in 1,105 households from the entire population of the Eastern Province, of which 86.6% of the children were Saudis. The average number of children younger than five-years-of-age per family was 1.81. Overall diarrhea prevalence was 7.6%/two weeks (Table 1). Age and sex distribution of children younger than five-years-of-age with diarrhea is shown in Table 2. Children younger than one-year-of-age constituted 29%.

The Chi-square test was applied to test for significance of difference between diarrhea morbidity and different variables (age group, occupation of head of the family, mother's education, type of housing, source of water, water storage, presence of animals, and type of latrine). The significant variables and diarrheal morbidity are noted in Table 3.

From Table 4, it is observed that the use of oral fluids was 69% but during a diarrhea episode, the use of ORS was only 23%. The association of feeding practices and diarrheal episodes in the children younger than two-years-of-age is shown in Table 5. Breast-fed children have fewer episodes as compared to those using formula feeding or other foods.

TABLE 1. *Distribution of population surveyed and diarrheal morbidity.*

	No. of households	Total < 5 pop.	Average < 5 child/family	No. of diarrhea cases	Period prevalence
Saudi	925	1,738	1.88	133	7.6
Non-Saudi	180	267	1.48	20	7.5
Total	1,105	2,005	1.81	153	7.6

$$\text{2-week diarrhea incidence rate} : \text{2-week diarrhea prevalence} \times \frac{14}{14 + \text{average duration of diarrheal episode}}$$

$$= 7.6 \times \frac{14}{14 + 3.5} = 6.0\%$$

$$= .060 \text{ episode/child}$$

Annual diarrhea cases = 90,447 cases

Total during the month of survey = 5,503 cases

$$\text{Seasonality adjustment factor} = \frac{5{,}503}{2} \div 9{,}0447 = 0.030$$

$$\text{Annual incidence} = \frac{0.060}{0.030} : 2.0$$

$$= 2.0 \text{ cases/child/year}$$

TABLE 2. *Age and sex distribution of* < 5 years children with diarrhea.

Age group	Male	Female	Total
< 6/12 months	4 (33.3)	8 (66.7)	12 (7.6)
6–12/12 months	20 (60.6)	13 (39.4)	33 (21.6)
13–36/12 months	35 (51.5)	33 (48.5)	68 (44.4)
37–60/12 months	20 (50.0)	20 (50.0)	40 (26.1)
Total	79 (51.6)	74 (48.4)	153 (100.0)

TABLE 3. *Diarrheal morbidity in children under five years of age by statistically significant variables.*

Variables	Morbidity	Total no. of children
1. Age group		
< 6/12 months	12 (6.2)	193
6–12/12 months	33 (14.6)	226
13–36/12 months	68 (8.2)	852
37–60/12 months	40 (5.4)	734
$X^2$19.7 Df 3 $P < 0.005$		
2. Housing		
a. Villa	79 (7.1)	1,113
b. Flat	67 (8.5)	789
*c. Temporary/shed	4 (13.8)	29
d. Tent	3 (4.0)	74
*$P < .01$		
3. Storage of water		
a. Earthen pitchers	8 (17.0)	47
b. Plastic containers	46 (6.0)	767
c. Metal containers	44 (9.1)	485
d. Concrete	14 (6.6)	211
e. No reservoir	41 (8.3)	495
$X^2$8.92 Df 4 $P < 0.05$ (without Yates' correction)		
4. Type of latrine		
a. With flush	97 (6.8)	1,430
*b. Without flush	52 (10.2)	511
c. Modified pit latrine 0 (0)	4 (7.4)	54
d. No latrine	0 (0.0)	10
*$P < .05$		
5. Presence of animals		
a. Animal present	35 (16.6)	211
b. Animal not present	118 (6.6)	1,794
$X^2$3.62 NS		
6. Source of water		
a. Pipe	120 (7.4)	1,613
b. Well	5 (5.7)	87
c. Tanker	26 (8.8)	295
d. Spring	2 (2.0)	10
$X^2$2.26 NS		

TABLE 4. *Type of treatment during episode of diarrhea.*

Treatment given	No. of diarrhea cases
1. Homemade fluids	71 (46.4)
2. ORS	35 (23.0)
3. Drugs (antibiotics & anti-diarrheals)	41 (26.8)
4. Traditional medicine	2 (1.3)
5. Intravenous fluids	4 (2.6)
Total	153 (100.0)

TABLE 5. *Type of feeding and diarrheal morbidity in children younger than two years of age.*

Type of feeding	Diarrheal morbidity	Total children
Breast-feeding	10 (4.4)	225
Breast-feeding + bottle feeding	18 (10.6)	170
Bottle feeding	20 (14.1)	142
Bottle feeding + other foods	37 (13.0)	284
Total	85 (10.3)	821

X^2 17.26 Df 3 $P < 0.005$

Discussion

One hundred fifty-three cases of diarrhea were detected during the two-week survey period. The overall prevalence of diarrheal disease was 7.6%/two weeks. The annual incidence was two episodes/child/year which is higher than the results shown in an earlier study conducted in Saudi Arabia [6], but close to the incidence reported by WHO [7]. However, the incidence is lower than results reported from other studies in underdeveloped countries [8–11]. The incidence would have possibly been higher if the survey had been conducted during the summer months. The duration of diarrhea lasted between two to five days (average 3.5 days). The majority of children with diarrheal disease were in the younger than three-year-of-age group, the recognized high risk group. Age was a significant factor in the prevalence of diarrheal disease ($P < 0.005$) (Table 3). Age specific prevalence of diarrhea was higher in the 6–12 month age group which correlates with other studies [12,13]. The increased susceptibility of this age group to the diarrheal disease can be explained by the decline in the passive immunity and increased exposure to the diarrheal agents at this age. While comparing diarrheal morbidity with other variable factors, it was observed that the type of housing, storage of water, and type of latrine was significantly associated with the prevalence of diarrheal disease. Hygienic practices and storage of water are important factors associated with diarrheal disease. Children consuming spring water and those living in households having animals show a higher morbidity of diarrhea, but the differences were not statistically significant. Other variables such as mother's education and occupation of the head of the family did not show any significant relationship with the prevalence of diarrheal disease.

In regard to treatment practices, 26.8% of the diarrhea cases received drugs (antibiotics and anti-diarrheals) in the health facilities where 60% of the total diarrhea cases were treated. This is probably because of the easy access and availability of the network of health centers which differs from other developing countries where there are fewer health centers with less accessibility. During an episode of diarrhea, 46.4% of the diarrhea cases used homemade fluids (including rice water and salt sugar solution) as treatment. ORS was used by 23% of diarrheal cases which indicates the need for an effective education program to increase the use of appropriate and available rehydration solutions.

Among the diarrhea cases reviewed during the survey, only 36% of those younger than two-years-of-age continued some feeding during the episode. The morbidity was lower in breast-fed children and there was a significant association between bottle feeding and the occurrence of diarrheal disease ($P < 0.005$). Our study concurs with other reports which have documented the protective role and the reduced risk of diarrheal disease in breast-fed children, especially those younger than six-months-of-age [14,15].

In conclusion, we believe: 1. Diarrheal disease continues to be a major problem, particularly in children younger than five-years-of-age; 2. The risk of diarrheal disease in these children and burden on health services can be reduced by increasing health education to promote awareness in mothers about proper feeding practices, particularly breast-feeding, personal, and environmental hygiene; 3. The efficacy of ORS therapy is well established, but its use is inadequate. A study to identify causes of low utilization, including behavioral and cultural block, is needed; and 4. To make the Control of Diarrheal Disease (CDD) program successful, frequent and continuous training programs are recommended to keep physicians and other health care workers motivated and aware of developments in the management and control of diarrhea disease.

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THE FREQUENCY OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE PHENOTYPES AND SICKLE CELL GENE IN AL-QASSIM

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أجريت هذه الدراسة في منطقة القصيم الواقعة في المنطقة الوسطى من المملكة العربية السعودية لتقدير تواتر عوز الإنظيم G-6-PD ومستويات هذا الإنظيم. أمكن التعرف على حالتين فقط من حملة الخلة المنجلية (Hb As) وبلغ تواتر جين Hb ٠,٠٠٠٩٨٥ . كان الإنظيم الطبيعي هو G-6-PD-b+ الذي بلغ تواتره ٠,٩٤٤ و ٠,٩٦٦ لدى جمهور الذكور وجمهور الإناث على التوالي. وتم التعرف على أنماط مغايرة أخرى شملت G-6—PD-A+ و G-6-PD ـ المتوسطية و G-6-PD-A— و G-6-PD ـ شبه المتوسطية بتواتر قدره ٠,٠١٦٤ و ٠,٠٢٨٢ و ٠,٠٠٢٣ و ٠,٠٠٩٤ لدى الذكور و ٠,٠٠٦٨ و ٠,٠٠٨٥ وصفر و ٠,٠١٠٢ لدى الإناث على التوالي. كان عوز G-6-PD الشديد ناتجًا بصفة رئيسية عن G-6-PD ـ المتوسطية وأمكن التعرف على ذكر واحد فقط لديه النمط G-6-PD-A— (٠,٠٠٢٣). وتظهر هذه النتائج أن تواتر جينات Hbs وعوز G-6-PD في منطقة القصيم أقل من جميع المناطق الأخرى في المملكة العربية السعودية التي تم تقصيها حتى الآن.

This study was conducted in the Al-Qassim area located in the central province of Saudi Arabia in order to estimate the frequency of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and sickle cell genes (Hb S). Blood samples from 1,015 Saudi males and females were analyzed for hemoglobin types, G-6-PD phenotypes and G-6-PD levels. Only two cases heterozygous to Hb S (ie Hb AS) were identified and the frequency of Hb S gene was 0.000985. The normal G-6-PD was G-6-PD-B+ occurring at a frequency of 0.944 and 0.966 in the male and female population, respectively. Variants identified included G-6-PD-A+, G-6-PD-Mediterranean, G-6-PD-A-, and G-6-PD-Mediterranean-like at frequencies of 0.0164, 0.0282, 0.0023, 0.0094 in the males and 0.0068, 0.0085, 0, 0.0102 in the female population, respectively. The severe G-6-PD deficiency was due mainly to G-6-PD Mediterranean and only one male with G-6-PD-A- (0.0023) was identified. These results showed that Al-Qassim had the lowest frequency of Hb S and G-6-PD deficiency genes compared to all other regions of Saudi Arabia that have been screened thus far.

Sickle Cell (Hb S) and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency genes were first reported in the eastern province of Saudi Arabia during 1960 [1,2]. Later, a number of epidemiological studies in different regions of the country showed a high prevalence of Hb S and G-6-PD deficiency genes particularly in the malaria endemic regions [3–10]. Studies were also conducted to investigate the G-6-PD variants [10,11–15], interactions between the two genes [16–18] and to determine their clinical presentations [19–22]. More extensive microscreening studies showed several major foci of these two genes and wide variations in the gene frequencies even within closely situated regions were encountered [23–25].

In an attempt to investigate the previously unscreened areas, we conducted this study on Saudi males and females in the Al-Qassim area in the central province of the country which is classified as a non-malaria endemic region. This paper reports our findings and compares the results obtained in Al-Qassim with those reported in other regions of Saudi Arabia.

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Material and Methods

This study was conducted in Al-Qassim shown in the sketch map of Saudi Arabia (Figure 1). The individuals included in this investigation were Saudi males and females attending the outpatient clinics of Ministry of Health (MOH) hospitals and dispensaries for minor illnesses. All individuals were original inhabitants of Al-Qassim. History was taken and physical examination was carried out by a physician and the information was recorded on special forms. Blood (5 to 10 ml) was drawn in ethylene diamine tetra acetate (EDTA) or acid-citrate-dextrose (ACD) tubes by venepuncture. The fresh blood was analyzed for the hematological parameters using a Coulter Counter ZF6 with a hemoglobinometer attachment. The red cells were separated from the plasma and the buffy coat by centrifugation and washed twice with cold physiological saline. Hemolysates were prepared just before analysis by addition of distilled water or 0.02% digitonin. The freshly prepared hemolysate was used for the separation of hemoglobin types by electrophoresis on alkaline and acid pH using previously published procedures [26,27]. The activity of G-6-PD was estimated spectrophotometrically in the hemolysate using commercially available kits (Boehringer-Mannheim Diagnostics). The change in optical density at 340 nm per minute at 35°C was estimated using a test solution containing 2.0 ml of triethanolamine buffer, pH 7.6, and EDTA (5 mmol/1), 0.1 ml of 10 mmol/1 nicotinamide adenine dinucleotide phosphate (NADP+), 0.1 ml glucose-6-phosphate (31 mmol/1) and 0.1 ml of the hemolysate. The units of G-6-PD (mU/109 erythrocytes/ml) were estimated for each sample.

The phenotypes of G-6-PD were separated by electrophoresis on cellulose acetate plates (Titan III, Helena Cat. No. 3023) at pH 8.6 using Supra Heme buffer (pH 8.6) for 20 min applying 350 V. Specific staining was conducted to visualize G-6-PD bands using G-6-PD staining reagent (Helena Cat. No. 5620) for 20 min at 20°C. The G-6-PD bands appeared as blue bands against a white background. The plates were fixed in 7.5% Trichloroacetic acid (TCA) for 2 to 3 min, washed with 5% acetic acid, air-dried and stored in plastic bags. Each plate was scanned on Helena Quick Scan densitometer.

The male and female samples were analyzed separately and frequency of G-6-PD phenotypes and G-6-PD deficiency were calculated separately for the two sexes.

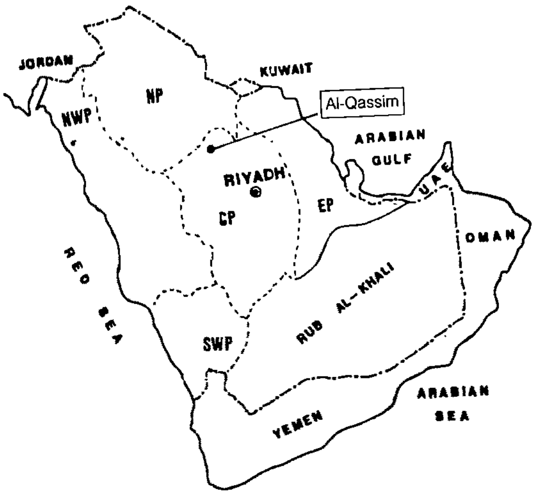

FIGURE 1. Map of Saudi Arabia.

Results

Of the total 1,015 samples analyzed during this investigation, only two cases heterozygous to Hb S gene (ie Hb AS) were identified. Both cases were unrelated females from the Al-Qassim area. The prevalence of Hb AS was 0.197% and the gene frequency of Hb S gene calculated using:

$$\frac{2 \times \text{No. of SS} + \text{No. of AS}}{2 \times \text{Total No. investigated}} \text{ was } = 0.000985.$$

The phenotypes of G-6-PD identified included G-6-PD-B+, the normal enzyme and variant with normal activity G-6-PD-A+. The severely deficient variants included G-6-PD-Mediterranean

TABLE 1. *Frequency of Hb S, severe and partial G-6-PD deficiency in the population of Al-Qassim.*

Genes	Sex	No. investigated	Frequency
Hb S	M&F	1,015	0.000985
Severe G-6-PD	M	426	0.0305
Deficiency	F	589	0.0085
Partial	M	426	0.0094
G-6-D deficiency	F	589	0.0102

TABLE 2. *Frequency of G-6-PD phenotypes in the population of Al-Qassim.*

Sex	Total no. invest-igated	Frequency of G-6-PD phenotypes					
		G6PD-B+	G6PD-A+	G6PD-Med	G6PD-A-	G6PD-Medlike	G6PD-B^+/A^+
Male	426	0.944	0.0164	0.0282	0.0023	0.0094	–
		(402)	(7)	(12)	(1)	(4)	
Female	589	0.966	0.0068	0.0085	–	0.0102	0.0085
		(569)	(4)	(5)	–	(6)	(5)

The number in the brackets is the no. of individuals.

and G-6-PD-A- (the African variant) and the partial deficiency was due mainly to a variant/s with mobility similar to G-6-PD-B+ but activity ranging between 20% to 60% of the normal enzyme. This variant was called the G-6-PD-Mediterranean-like variant. Five females were identified who were heterozygous to G-6-PD-B+ and A+. The frequency of HbS, severe and partial G-6-PD deficiency in the male and female population is presented in Table 1. The frequency of the various G-6-PD phenotypes in the male and female population is presented in Table 2. The expected frequency in the females calculated applying the Hardy-Weinburg equilibrium was 0.000795. This was higher than the actual frequency observed (0.0085) in the females of Al-Qassim. In an attempt to compare the gene frequencies in Al-Qassim with those reported in other regions, Tables 3 and 4, summarize Hb S and G-6-PD deficiency gene frequencies encountered in other regions in Saudi Arabia.

Discussion

Al-Qassim lies on a flat land-table in the central province of Saudi Arabia and has several oases distributed in and around it. However, due to low atmospheric humidity throughout the entire year, the environment does not provide an ideal breeding site for the anopheline mosquitoes which do not survive long enough to become infective to human victims. Thus, in Al-Qassim and surrounding areas, no measurable malaria endemicity has ever been established [28].

As shown by the results in this study, Al-Qassim has the lowest gene frequency of Hb S and G-6-PD deficiency genes compared to all other regions of Saudi Arabia thus far investigated. The highest frequency for Hb S gene has been reported in Al-Qatif while the lowest frequency thus far was in Riyadh, located in the central province and a non-malarious area [28]. This is also true for G-6-PD

TABLE 3. *Hb S gene frequency in different regions of Saudi Arabia*.*

Province	Area	Hb S gene frequency
Eastern	Al-Qatif	0.1741
	Al-Hofuf	0.150
	Dammam	0.0524
Central	Riyadh	<0.010
Northwestern	Khaiber	0.083
	Al-Ula	0.81
Western	Al-Qunfuda	0.115
	Yanbu	0.0155
	Al-Baha	0.0187
Southwestern	Jaizan	0.103
	Najran	0.183
	Bisha	0.0831

* [Ref 34]

TABLE 4. *The frequency of severe G-6-PD deficiency in the male population of Saudi Arabia in different regions.*

Province	Area	Frequency of severe G-6-PD deficiency	Ref.
Eastern	Al-Hofuf & villages	0.190	8
	Mansura	0.533	2
	Safwa	0.647	2
	Al-Ajam	0.655	2
Central	Riyadh	0.071	8
Western	Unspecified	0.041	2
	Al-Baha	0.128	10
	Al-Qunfuda	0.152	10
Southwestern	Jaizan & surrounding areas	0.205	8
Northwestern	Khaiber and surrounding areas	0.22	8

deficiency which is at the lowest frequency in Al-Qassim as compared to other regions of Saudi Arabia and is almost similar to that encountered in Riyadh (Table 4). G-6-PD-B+ is the normal enzyme in Al-Qassim, as has been reported in all other regions of Saudi Arabia and the variants with normal activity is G-6-PD-A+. This variant is encountered in most of the regions of Saudi Arabia at frequencies ranging from 0.0111 to 0.049 in the male population [10]. Severe deficiency is caused mainly by G-6-PD-Mediterranean and only one case of G-6-PD-A- was encountered. As in other regions, partial deficiency in Al-Qassim is caused by the variant/s which has yet to be characterized but is similar to G-6-PD-Mediterranean due to its mobility but differs in its activity.

These results confirm that a significant genetic heterogeneity exists in the different regions of Saudi Arabia and the frequency of both G-6-PD deficiency and Hb S gene show considerable variation. As noted earlier, regions of Saudi Arabia with a low frequency of G-6-PD deficiency also have a low frequency of Hb S gene [4,6,8]. In most regions, a close correlation exists between malaria and the genes for Hb S and G-6-PD deficiency. It has been shown in several studies that the carrier states of these genes provide a natural resistance against malaria and significant differences are usually found between Hb S heterozygotes and normal for the parasite rate and densities [29–33].

It is possible that in Al-Qassim the Hb S and G-6-PD deficiency genes may not have appeared by mutation or by migration to such an extent as to allow these genes to establish in high frequency. Furthermore, since one of the known selective force i.e. malaria, is not present in Al-Qassim, the genes have not established in any significant frequency. The few cases that have been identified as having Hb S and G-6-PD deficiency may have been the result of genetic drifts and gene flow from malarious regions. Further studies are necessary in other regions of Saudi Arabia in order to identify factor/s which may be contributing to an increase in the frequency of G-6-PD deficiency and Hb S genes in this population.

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A COMPARATIVE STUDY OF IMMEDIATE SKIN TEST REACTIVITY TO INHALANT ALLERGENS IN ASTHMATIC CHILDREN OF TWO DIFFERENT REGIONS IN SAUDI ARABIA

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تم مقارنة تفاعلات أختبار الجلد لمستأرجات الاستنشاق المختلفة لدى أطفال ربويين من منطقتين مختلفتين في المملكة العربية السعودية. اخترنا لذلك مئة وعشرين طفلاً من كل من المنطقتين الغربية والوسطى يمثلون ملامح بيئية مختلفة. تم تحليل تفاعل أختبار الوخز لأربع وعشرين مستأرجا ومقارنتها. أظهر واحد وسبعون مريضًا (٥٩,٢٪) من الرياض (المنطقة الوسطى)، تفاعلات جلدية إيجابية لمستأرج واحد أو أكثر، بينما أبدى سبع وثمانون مريضًا (٧٢,٥٪) من مكة المكرمة (المنطقة الغربية)، تفاعلات إيجابية لمستأرجات مختلفة. أظهر توزيع حساسية أختبار الجلد فروقًا واضحة بين المجموعتين، كان أبرزها التفاعلات لسوس غبار المنازل من نوع (D. Farinae) الذي كان مسؤولاً عن نسبة ٥٦,٣٪، وللمستأرجات الفطرية (٣١,١٪) لدى الربويين في المنطقة الغربية، بينما كانت التفاعلات للمستأرجات نفسها في المنطقة الوسطى ١٠٪ و ٥,٨٪ على التوالي. كما شوهدت اختلافات ملحوظة فيما يتعلق بمستأرجات غبار الطلع بلغت نسبتها ٩,٣٪ في المنطقة الوسطى و ١٥,٤٪ في المنطقة الغربية. تشير الدراسة إلى وجود أنماط مختلفة للمستأرجات في المنطقتين كما تشير إلى العوامل المناخية والبيئية وتأثيرها على تحسيس من لديهم استعداد للتأثر.

The skin test reactivities to various inhalant allergens in asthmatic children from two different regions in Saudi Arabia were compared. One hundred-twenty subjects each from the Central and Western regions, representing different environmental features, were selected. Prick test reactivity to 24 common allergens were analyzed and compared. Seventy-one (59.2%) patients from Riyadh (Central region) showed positive skin reactions to one or more allergens, while 87 (72.5%) reacted positively to different allergens from Makkah (Western region). The distribution of skin test sensitivity revealed striking differences in the two groups. The most prominent were reactions to the house dust mite (*D. farinae*) which amounted to 56.3% and to fungal allergens, 31.1% in asthmatics from the Western region, while reactions to the same allergens in subjects from the Central region were 10% and 5.8%, respectively. Similarly, marked variations were noted with pollen grain allergens with 9.3% in Central region and 15.4% in the Western region. The study indicates the presence of different allergen profiles in the two regions and suggests the influence of climatic and environmental factors and their impact on sensitization of susceptible subjects.

Bronchial asthma in children is a common disease in Saudi Arabia with up to 11.5% children, nationally, having wheeze [1,2]. The disease varies from region to region and extrinsic factors are considered to be important in the sensitization of susceptible individuals and in the elicitation of their symptoms [3,4]. It is well documented that environmental factors are more significant than genetic factors in development of allergic disease [5]. Based on this, attempts have been made to prevent the onset of disease by avoidance of provoking factors [6]. This depends on knowledge about the prevalent allergens in different localities as well as their identification in subjects. Many diagnostic probes are available. However, the

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skin prick test method is preferred because of its ease of performance, high degree of reproducibility, and better correlation with in vitro measurements [7,8].

The present investigation was undertaken to determine the pattern of immediate type hypersensitivity reaction in asthmatic children to a common panel of inhalant allergens in two different geographically and climatologically regions of Saudi Arabia.

Material and Methods

Subjects

One hundred-twenty children, each from Riyadh (Central region) and Makkah Al Mukkaramah (Western region) were included in the study. These were asthmatic children attending the Pediatric Allergy Clinic at King Khalid University Hospital (KKUH), Riyadh and the Pediatric Clinic at Umm-Al-Qurah University Health Center, Makkah. Riyadh, the capital city of Saudi Arabia, is situated in the middle of desert with dry and hot weather. Makkah, an ancient city, is situated within 100 km from the coastal city of Jeddah and from the Red Sea with comparatively humid and hot weather. Only children between 6 to 13 years of age were included in the study. Each child was earlier diagnosed by a physician as suffering from bronchial asthma following a full history and clinical examination.

TABLE 1. *List of SPT allergens with quality and concentration.*

	Species	Common name	Concentration (W/V)
Indoor	Cladosprorium herbarium		1:20
	Cat fur SQ**		10 HEP*
	Dog hair SQ**		10 HEP*
	Dermatophagoides farinae SQ**		10 HEP*
	Cotton flock		1:20
Fungi	Alternaria alternata		1:20
	Cladosprorium herbarium		1:20
	Rhizopus nigricans		1:20
	Phoma herbarum		1:20
	Ulocladium chartarum		1:20
	Aspergillus fumigatus		1:20
	Aspergillus niger		1:20
Pollen	Acacia SP		1:100
	Chenopodium album	Lamb's quarter	1:100
	Plantago major		1:100
	Artemisia vulgaris	Mugwort	1:100
	Salix caprea	Willow	1:100
	Hordeum sativum	Barley	1:100
	Pragmites communis	Reed	1:100
	Zea mays	Corn	1:100
	Cynodon dactylon	Bermuda grass	1:100
	Poa Pratensis	Rapgrass SQ**	10 HEP*
	Lolium perenne	Ryegrass SQ**	10 HEP*
	Phleum pratense	Timothy SQ**	10 HEP*

* HEP indicates in vivo histamine-related standard.
** SQ indicates special purity.

SPT Allergens

All patients were skin prick tested (SPT) with a set of inhalant allergens (24) obtained from Allergologisk Laboratiorium (ALK), Denmark. The allergen extracts were grouped into pollen allergens including tree, grass, and weeds: fungal spore allergens including a range of species indentified from spore traps in the region and indoor allergen group including insects, house dust mite (*D. farinae*) and animal danders (dog hair and cat fur), and cotton flock (Table 1). Materials for skin testing were selected as representing the most common regional allergens from our studies in the region [9–12]. All SPT was conducted using standardized special purity (SQ) materials where possible. A small number of samples were also purchased from Greer Laboratories, USA. A positive control with histamine (1 mg/ml) dihydrogen phosphate and a negative control with glycerin saline were included in the test panel.

Method

A standard SPT method was used where a drop of the allergen solution was applied on the forearm and the skin pricked through the drop with a lancet obtained from B-D, microlance. Excess solution was then blotted off and results recorded after 15 minutes. The test was considered positive when the wheal diameter measured 3 mm or more. For the purposes of comparison, results were graded according to the wheal diameter into negative (<3 mm); positive, mild (3 mm); moderate (3–5 mm); and strong (> 5 mm).

Forty-eight hours prior to skin testing, patients discontinued antihistamines and those on long-term corticosteroid therapy were excluded.

Results

Seventy-one (59.2%) of 120 asthmatic children from the Central region (Riyadh) and 87 (72.5%) of 120 patients from the Western region (Makkah) showed positive skin test reactions to one or more allergens (Table 2).

The mean percentage and range of positive skin reactions to various groups of allergens is shown in Table 3.

Skin reactions to various indoor allergens for both patient groups are shown in Figure 1. Asthmatic children from Makkah showed frequent positive reactions to *D. farinae* followed by cat fur, cotton flock, cockroach, and dog hair.

Figure 2 shows the distribution of reactions to seven different fungal spore allergens. Asthmatics (31.3%) from the Western region showed positive sensitivity compared to 5.8% from the Central region.

Reactions to 12 pollen grain allergens are shown in Figure 3. More children reacted to *Lolium perenne* (Rye grass) and *Cynodon dactylon* (Bermuda grass) in both groups. Reactions to *Acacia, Zea mays* (corn), and *Artemesia vulgaris* (Mugwort) were more prominent in asthmatics from the Makkah region.

Discussion

It is well documented that IgE-mediated diseases involve a variety of mechanisms, some of which have a genetic basis [6]. However, the onset of clinical symptoms are due to interaction of susceptible individuals with environmental factors. Identification of these factors is necessary to allow the development of methods to prevent allergies.

The interaction and influence of environmental factors is well demonstrated in this study. The total number of positive skin responses was higher in patients from Makkah (Western region) compared to Riyadh (Central region). This confirms the earlier observation that the prevalence of asthma and rhinitis is higher in the Western region of Saudi Arabia. Striking differences were observed in skin reactions to fungal spores, pollen grain allergens and to the house dust mite, *Dermatophagoides farinae. D. farinae* was the most important indoor allergen in patients in the Western region while it played a less important role in

TABLE 2. *Comparison of overall positive reactions to various allergen groups in Riyadh and Makkah regions.*

	Riyadh	Makkah
Total patients tested	20	120
No. of positive patients	71	87
% of positive patients	59	73

TABLE 3. *Mean percentage and range of positive skin reactions* to various groups of allergens in asthmatic children in Riyadh and Makkah.*

	Riyadh (%)	(Range) (%)	Makkah (%)	(Range) (%)
Indoor allergens group R = 7** M = 5	32.6	(8.4–71.8)	43.9	(28.7–56.3)
Fungal allergens group R = 7 M = 7	5.8	(1.4–15.4)	31.3	(10.3–40.2)
Pollen allergens group R = 13 M = 17	9.3	(4.2–25.4)	15.4	(8.0–29.9)

* Percentages of positive reactions for various allergen groups are based on total positive reactions and not on the total number of patients tested.

** R = Riyadh, M = Makkah; number of allergens for each group tested.

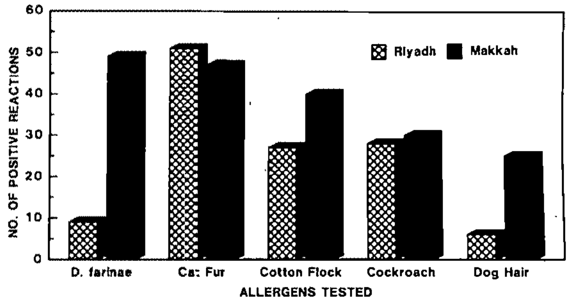

FIGURE 1. Positive skin reactions to various indoor allergens in asthmatic children in Riyadh and Makkah regions.

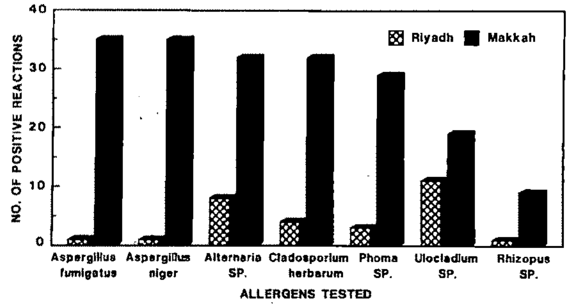

FIGURE 2. Positive skin reactions to various fungal allergens in asthmatic children in Riyadh and Makkah regions.

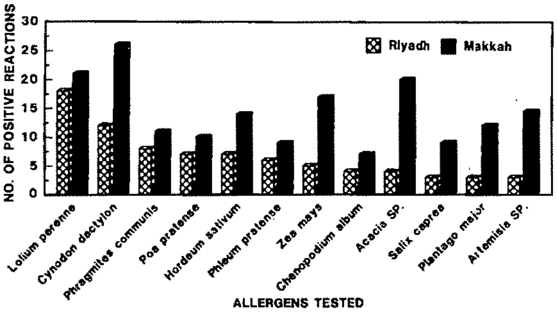

FIGURE 3. Positive skin reactions to various pollen allergens in asthmatic children in Riyadh and Makkah regions.

patients in the Central region. Sensitivity to cat fur was prominent in patients in the Riyadh region and was the second important allergen in patients from Makkah. The response to cat fur allergens was not paralleled by positive history of contact with domestic cats as the majority of patients denied direct contact with cats. Reactions to cockroach allergens and cotton flock were observed in both localities. It is worth mentioning that cockroach sensitivity is increasingly encountered in our patients and may turn out to be an important etiologic agent in causing perennial symptoms [13]. This prompted us to prepare a local extract for comparison with the commercially available cockroach allergens. The study is in progress and will be subject to subsequent communication.

On the other hand, skin reactions to fungal spore allergens showed major variations in two regions.

More patients reacted to fungal allergens from the Western region. Patients mostly reacted to *Aspergillus* species, *Alternaria, Cladosporium, Phoma* as well as to *Ulocladium* and *Rhizopus*. In the Central region asthmatic children reacted far less to fungal spore allergens. The prominent reactions were to *Ulocladium* and *Alternaria*. It is our impression, from previous aerobiological studies and analysis of dust from patients' homes, that fungal spores may be important outdoor as well as indoor allergens and may also be responsible for perennial symptoms. A comprehensive study on fungal allergy using locally prepared extracts is currently underway and preliminary results are encouraging.

Skin reactions to pollen allergens were also found to be more frequent in patients from the Western region. Asthmatic children frequently reacted to *Cynodon dactylon* (Bermuda grass), *Lolium perenne* (Rye grass), *Acacia, Zea mays* (Corn), and *Artemesia vulgaris* (Mugwort). In the Central region, more reactions to *Lolium perenne* (Rye grass) and *Cynodon dactylon* (Bermuda grass) were observed. Skin reactions to *Acacia, Zea mays* (Corn), and *Artemesia vulgaris* (Mugwort) were far less frequent.

In conclusion, it appears that aerobiological studies are important prerequisites for proper management and prevention of allergic disease. The Kingdom of Saudi Arabia is a large country with different environmental features. It seems important to perform similar studies in other regions in order to set up a national allergen profile. This will be of practical value for the management and prevention of allergic diseases. The study also indicates that a high proportion of allergic individuals have IgE antibodies against the allergens tested and they may be "at risk" to manifest symptoms if re-exposed to these allergens.

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THE SEASONALITY OF MANIA: PRELIMINARY FINDINGS

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أجري استقصاء للعلاقة بين المتغيرات المناخية وحالات الهوس التي أدخلت إلى أحد المستشفيات التعليمية في الرياض في المملكة العربية السعودية على مدى ست سنوات. وقد أشارت النتائج إلى وجود ترابط ضعيف ذي أهمية بين معدلات الإدخال الشهرية لحالات الهوس مع طول اليوم والرطوبة وضغط الهواء ودرجة الحرارة. لكن لم يظهر هذا الترابط من القوة ما يكفي للايحاء بوجود نزعة موسمية. كما أن المتغيرات المناخية للشهر الحالي هي أفضل ترابطاً منها في الشهور السابقة. إن وفرة أشعة الشمس طوال السنة قد يوضح ضعف الترابط بين المتغيرات المناخية وحالات الهوس التي تدخل إلى المستشفى وذلك خلافًا للتقارير التي ترد من البلاد الأخرى.

The relationship between climatic variables and monthly manic admissions to a teaching hospital in Riyadh, Saudi Arabia was examined over a six-year period. The results indicate a weak but significant correlation between monthly admission rates of mania and day length, humidity, air pressure, and temperature. The correlation did not seem, however, to be strong enough to indicate a seasonal trend. Also, current month climatic variables are better correlated than previous months. The prevalence of sunshine throughout the year may explain the low correlation with mania admissions unlike reports from other countries.

The onset or relapse of affective disorders have been reported to relate to seasonal variations [1]. Studies of suicide (being heavily contributed to by major depressive disorders), support these findings [2]. Studies of the seasonal incidence of affective disorders have demonstrated a tendency for spring and fall peaks of depression and a summer peak of mania [1]. A sex differential has also been observed. In fact, Symon and Williams [3] reported a seasonal variation for female manic admissions; the peak being in August-September, while for males they found no significant seasonal pattern. Walter [4], however, reanalyzed the Symon and Williams data and found significant seasonal variations for both sexes. Myers and Davies [5] reported on the seasonal incidence of mania and its relationship to climatic variables and found a significant annual cycle with a peak in summer and trough in winter, the current month temperature being the best predictor of mania admission rate. In the study conducted by Carney et al [6], the influence of climate on the prevalence of mania demonstrated a striking peak during spring and summer, with a decline in autumn and increase again during winter. They also found that sunshine and day length correlated significantly with mania admission rates while current month temperatures did not.

Our clinical experience in Riyadh suggests an increase in admission rates for mania during the winter months. Also, both the fact that the extremely hot climate of Saudi Arabia contrasts sharply with temperate climates in countries where previous studies have been conducted and the paucity of similar studies in hot regions prompted us to initiate this study. Therefore, our objectives were to verify whether there was a seasonal variation in the prevalence of mania in Riyadh and to examine the association between

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monthly mania admission rates and individual climatic variables.

Material and Methods

There are three psychiatric admitting facilities in Riyadh. One is strictly for military people while the other two are available for the general population. One of the two facilities is King Khalid University Hospital (KKUH), where this study was carried out. Cases of DSM III diagnosis of mania admitted to King Khalid University Hospital in Riyadh during the period 1984 to 1989 were retrospectively reviewed. The following parameters were assessed: demographic data, admission related information e.g., age at admission, number and duration of admissions, duration of the illness and drug status prior to admission, and family history of mental illness including affective disorders. Cases of schizoaffective disorders were excluded. Monthly records included averages of temperatures, rainfall, air pressure, day length and relative humidity as recorded at the meteorological station located in Riyadh during the six-year study period and plotted against the monthly rates of manic admissions. Series analysis using the autoregressive model was adjusted to investigate seasonal variations in temperatures, day length, and manic admissions. Correlations were measured using Spearman's rank order correlation coefficient. The student's t-test was used to investigate statistical significance of seasonal differences in monthly admissions at the 5% level. Finally, a stepwise multiple regression analysis was carried out to examine the joint effect of climatic variables on manic admissions [7].

Results

During the study period there were 84 patients; 55 males (66%) and 29 females (34%), and a total of 142 admissions; males included 89 (63%) and females 53 (37%). Forty-one patients (23 males and 18 females) had more than one admission. Table 1 shows the patients' ages during last admission. Prior to the last admission, 11 patients were on lithium maintenance therapy, 16 on neuroleptics, and 6 on antidepressants (Table 2). Twenty-four patients had a family history of affective disorders. The average duration of illness prior to admission was 1.3 weeks for males and 2.5 weeks for females. The average duration of hospitalization was 3.6 weeks for both sexes.

During 1984 to 1989, there appeared to be a monthly fluctuation in the frequency of admissions but an autoregressive integrated moving average model adjusted to the mania admission data suggested no dependence on seasons in both sexes. The autocorrelations were all within two standards on the plot. A Spearman's correlation matrix noting frequency of admissions and the climatic factors are shown in Table 3.

The correlation between temperatures, humidity, air pressure, day length, and frequency of mania admissions were low, but statistically significant ($P < 0.05$). In fact, day length and temperatures had a negative correlation with frequency of admission; the maximum temperatures were recorded between July and August and this cor-

TABLE 1. *Patients' age on last admission.*

Age (Years)	24	25–39	40–54	55–75	Total
Frequency	22	50	8	4	84
Percentage	26.2	59.5	9.8	4.8	100

TABLE 2. *Treatment (last admission).*

	Prior to admission	During hospitalization
None	50	0
Neuroleptics	16	41
LI	11	40
ECT	0	2
HCA	6	0
Others	1	1
Total	84	84

LI = lithium carbonate; ECT = electroconvulsive therapy; HCA = heterocyclic antidepressants.

TABLE 3. *Univariate Spearman correlation coefficient (r =) of mania admission frequencies and climatic factors.*

Climatic factor	Mania admission frequency	t-Value	Level of significance
Temperature	–0.21	–2.635	$P < 0.05$
Humidity	0.23	2.874	$P < 0.005$
Air pressure	0.26	3.292	$P < 0.001$
Rainfall	0.14	1.793	$P < 0.1$
Day length	0.22	–2.729	$P < 0.01$

Number of observations = 154.

responded with the low frequency of admission ($r = 0.21$, $P < 0.05$). A multiple stepwise regression analysis was carried out to assess the joint effect of climatic factors on the frequency of admission for mania. Temperatures, humidity, and air pressure combined explains only 16.7% of the total variation of patients admitted for mania. Analysis of variance showed the regression to be statistically significant (F-Ratio = 10.03 on 3,150 degrees of freedom, $P < 0.0001$). But, when the full model with interaction effects were adjusted, approximately 70% of the total variation in mania admission rates were explained by these climatic variables (Table 4). The analysis of variance to test the significance of regression coefficients presented an F-ratio of 46.50 on 7,146 degrees of freedom and statistical significance of ($P < 0.0001$). However, interpretations of the independent effects of the climatic factors are difficult because of the significant interaction effects.

An analysis of previous month's climatic variables including total admissions averaged during the six-year period showed poor negative correlations with temperatures, humidity, and rainfall ($P > 0.05$). But the correlation with barometric pressure was positive and statistically significant ($P < 0.05$). Also, the joint effect of the previous month's climatic variables explained approximately 50% of the variability in total admissions. The significance of the regression coefficients using these variables as independent and total admissions as dependent, investigated by the analysis of variance resulted in an F-value of 49.6 on 5,148 degrees of freedom ($P < 0.0001$). However, the result of the simple correlation analysis (Table 5) showed that current month climatic variables were better correlated with total admissions for mania than the previous month's variables.

TABLE 4. *Multiple regression coefficient of the relation of mania admission and climatic factor.*

Climatic factor	Regression coefficient	Standard error	t-Value	Level of significance
Constant	-4061249	3140.75	-12.931	$P < 0.0001$
Temperature	850.89	66.98	12.704	$P < 0.0001$
Humidity	1094.12	79.78	13.714	$P < 0.0001$
Air pressure	42.69	3.30	12.922	$P < 0.0001$
Temperature % Humidity	-22.74	1.54	-14.811	$P < 0.0001$
Temperature % Air pressure	-0.89	0.07	-12.677	$P < 0.0001$
Humidity % Air pressure	-1.15	0.08	-13.708	$P < 0.0001$
Temperature % Humidity % Air pressure	0.02	0.002	14.817	$P < 0.0001$

Multiple $R^2 = 0.83$, $R = 0.69$.

TABLE 5. *Spearman correlation coefficients of climatic variables.*

	Ptemp	Phumid	Ppress	Prain	Temp	Humid	Rain	Press	Adm.	Month
Ptemp	1.00									
Phumid	-.94	1.00								
Ppress	-.95	.87	1.00							
Prain	-.43	.62	.33	1.00						
Temp	.81	-.70	-.89	.01	1.00					
Humid	-.84	.74	.90	.14	-.95	1.00				
Rain	-.68	.64	.58	.38	-.48	.65	1.00			
Press	-.71	.60	.83	-.00	-.95	.87	.35	1.00		
Adm.	-.12	-.08	.25	-.10	-.21	.25	.11	.27	1.00	
Month	.60	-.64	-.36	-.58	.50	-.10	-.45	.07	.20	1.00

The *P* prefix indicates previous months climatic variables. Adm. is short for admission.

Discussion

The results of this study did not demonstrate a seasonal trend of mania as reported in the literature. Riyadh is located in the central region of Saudi Arabia with a hot dry desert climate. Winter and summer are the main seasons when temperatures drop to as low as –3°C during winter and reaches 46°C or higher during the summer, with scanty rainfall, plenty of sunshine during the whole year and variation of day length throughout the year. Little variability in variables other than temperature confirms Carney et al, findings that both sunshine and day length, but not temperatures, correlated significantly with admissions for mania rate [6]. The authors suggested that the onset or relapse of mania may be due to an abnormal response to increasing exposure to light. The results of our study suggest temperatures as the highest correlate with mania admissions followed by humidity and air pressure. Myers and Davies [5] argued that since temperature had the highest correlation with manic admission rates, it acts as a fine adjustment determining which month admission actually occurred.

The findings of the present study suggest that factors other than climate contribute to the onset or relapse of mania. The low admission rates for mania during the summer (July-August) corresponding to the period with the highest temperatures lends support to our impression that admission rates for mania increase during the winter months. These findings may be partly due to the Hajj (pilgrimage) operations and annual vacations during this time of the year. Since 27 patients were on maintenance therapy prior to last admission, one may hypothesize that maintenance therapy modifies or prevents the seasonal effect in the patients, but fails to act as a prophylactic. Male patients were over-represented in our sample. This is a frequently reported observation in hospital based studies in this country [8]. Female manics seem to be more tolerated by family members which is reflected by the longer duration of illness prior to admission. The finding that current month variables correlated better with monthly admission rates than previous month variables is also similar to that previously reported by Myers and Davies [5].

The present study is limited because it has been conducted in one of the three hospitals recruiting psychiatric patients in Riyadh, Saudi Arabia. However, in spite of the seemingly lack of seasonal variation in manic admission rates, a nationwide study may be desirable to further paint a clearer picture on the perspective.

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RECTUS ABDOMINIS MYOCUTANEOUS FLAP: ANALYSIS OF 40 CASES

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نعرض هنا سلسلة تضم ٤٠ مريضًا أجريت لهم عمليات ترميمة باستخدام وحدات عضلية جلدية من المستقيمة البطنية. كانت أنماط النسيج المنقول كما يلي: ذو سويقة علوية (٢٦ حالة)، وذو سويقة سفلية (١١ حالة)، وسدائل عضلية حرة (٣ حالات). توزعت الحالات التي طبقت فيها العملية على ثلاث مجموعات هي: (١) ترميم الثدي وجدار الصدر (٢) المناطق الإربية والتناسلية والمدورية (٣) قرحة الساق وعقب القدم. تظهر النتائج أن التسليخ الجراحي للسدائل سهل نسبيًا وله تطبيقات واسعة يمكن استخدامها في مشاكل الترميم الجراحي المختلفة. تعتبر نسبة وقوع مضاعفات التسليخ الجراحي ضئيلة وذلك فيما يختص بحيوية السديلة المنقولة أو ما يختص بالموقع الذي أخذت منه.

We present a series of 40 cases who underwent reconstructive procedures using rectus abdominis myocutaneous units. The transplanted tissue comprised superior pedicle (26 cases), inferior pedicle (11 cases), and as free muscle flap (3 cases). The application fell into three groups i.e.; 1. breast and chest wall reconstruction; 2. groin, genital, and trochanteric area; and 3. leg and heel ulcer. The results show that surgical dissection of flaps is relatively easy and has a wide range of applications that can be used for different surgical reconstructive problems. Surgical dissection has a low incidence of complications for flap viability as well as for donor site.

Rectus abdominis myofaciocutaneous units based on the superior and inferior deep epigastric system and its perforators are reliable for both pedicle and free transfers [1–3]. This review presents our clinical experience using different types of rectus abdominis myofaciocutaneous units. Their advantages and disadvantages are highlighted.

Clinical Material

Between April 1983 and November 1991, 40 patients underwent reconstructive procedures using rectus abdominis myocutaneous unit in the Plastic Surgery unit at King Fahd Hospital of the University, Al-Khobar, Saudi Arabia. There were 26 females and 14 males; their median age was 37 years. All patients were followed from two months to seven years, with a mean of three years.

Transplanted Tissue

The transplanted tissue comprised of superior pedicle rectus myocutaneous flap (26 cases), extended inferiorly pedicled myocutaneous flap (11 cases), rectus muscle free flap (3 cases), based on inferior epigastric vessel anastomosis. Applications fell into three groups (Table 1): 1. Breast and chest wall reconstruction (26 cases): Of the 26 patients in this group, 15 required reconstruction of the breast following modified radical mastectomy (Figures 1 and 2); two cases of radionecrosis of the chest wall necessitated extensive chest wall and rib excision. The flap measured 35 × 25 cm in diameter. Six patients having breast reconstruction had had either a full course of chemotherapy and/or radiotherapy. In ten cases, reconstruction was performed after 1½ - 2 years, while in five cases, reconstruction was performed immediately (as a combined procedure with mastectomy). There were two cases of post-burn adherent

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breast, after release of contracture breast tissue as augmented by autogenous tissue of rectus abdominis myocutaneous flap; 2. Groin and genital area (11 cases): Four cases of post-traumatic exposure of the hip bone presented with severe infection. Three cases of tumor ablation of groin fibrosarcoma received a course of deep radiotherapy to the lesion in the groin followed by ulceration; one case infiltrating the femoral artery necessitated saphenous vein graft (Figure 2). The flap size in this group was 25 × 20 cm in diameter; and 3. Leg and heel ulcers (3 cases). Four cases of post-traumatic ulcers of lower one-third of the leg and heel (Figure 3) had severe compound injury of the leg associated with compound fracture of the tibia and calcanous. Angiography of the cases revealed patency of all vessels. After repeated debridement of the wound, stabilization of the fracture with an external fixation device, the defects were closed by free muscle with application of split skin graft covering the wound.

TABLE 1. *Flaps used and diagnoses.*

Flap and reconstruction	Diagnosis	N
Superior pedicle myocutaneous for breast and chest	– Carcinoma of breast	15
	– Post-burn adherent breast	2
	– Chest wall radionecrosis	3
	– Tumor ablation (fibrosarcoma)	6
		26
Inferior pedicle for groin and genital areas	– Fibrosarcoma (groin region)	4
	– Post-traumatic raw area hip and upper thigh	5
	– Penile and urethral reconstruction	2
		11
Free muscle for leg and heel ulcer	– Traumatic leg ulcer	2
	– Traumatic heel ulcer	1
		3
Total		40

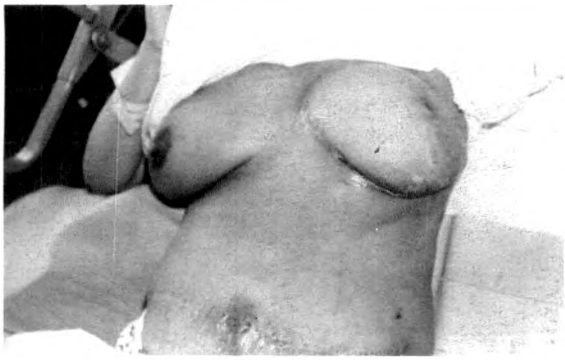

FIGURE 1: A 37-year-old female following mastectomy with moderate obesity and a large pendulous breast on the healthy side. Reconstruction using transverse rectus abdominis myocutaneous flap with primary closure of donor site.

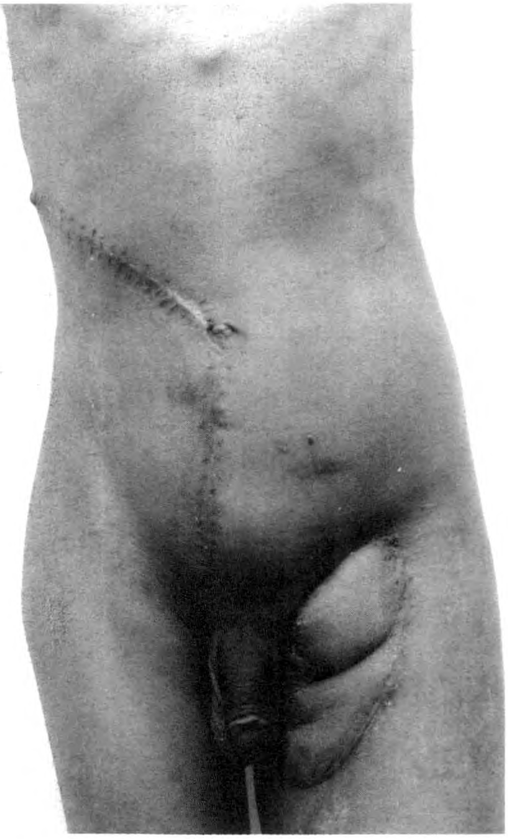

FIGURE 2: A contralateral rectus abdominis inferior pedicle flap covering a defect of excised fibrosarcoma groin region.

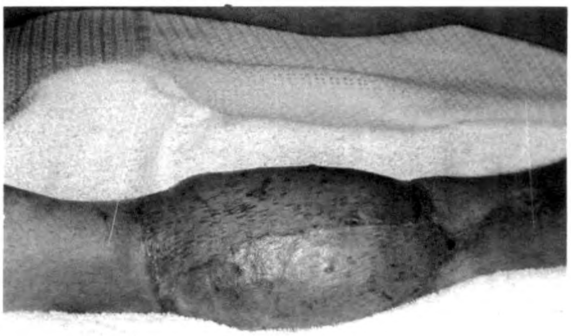

FIGURE 3: The compound injury at lower third or leg reconstructed with a mesh skin-grafted rectus abdominis free-tissue transfer. The result at three months.

Results

More than 80% of the patients in this series were obese and 50% were smokers. There were no perioperative deaths. One patient developed adult respiratory distress syndrome and was successfully managed and none developed deep vein thrombosis.

Flap Survival

No patients suffered total flap loss. Two patients developed partial flap necrosis. In one case of transverse superior pedicle rectus myocutaneous flap, there was partial flap necrosis in the contralateral (distal) part. In another case with free myocutaneous flap based on inferior epigastric vessels, the distal part showed ischemia on the third postoperative day where an extensive hematoma was discovered underneath.

Donor Site

Most of the donor sites healed by first intention; whether closed directly (33) or by split skin graft (7). In superiorly based flap and in free muscle flap the scar healed well in the suprapubic area (inconspicuous area). However, in the inferior pedicle cases, the scar became more apparent especially over the chest wall. Only one patient developed abdominal weakness (bulge) postoperatively where the flap had been taken down to arcuate line. No Marlex patch or other synthetic material to reinforce abdominal facial closure was used in this series. On three occasions, hematoma developed which was evacuated by repeated aspirations.

Healing Time and Hospitalization

The time required for soft tissue to heal and the length of hospital stay showed no significant difference. In the superior pedicle and in the free muscle group, healing time and hospitalization rquired (10 + 5 days) while (20 + 5 days) was necessary in the inferior pedicle flap group ($P > 0.01$).

Patient Satisfaction

Patients were followed for various periods after reconstruction regarding satisfaction with reconstruction procedure, presence of scar in conspicuous areas. They were rated as very satisfied, satisfied or disappointed. The patients with breast and penile reconstructions were pleased with the overall results. General appearance and emotional state were rated as improved by 95% of the patients. In 90% of cases the patients with inferiorly based flap for reconstruction of groin or trochanteric area where skin graft was used for donor site closure were satisfied. Most of these patients were very old and reconstruction was performed for oncological problems.

Discussion

The rectus abdominis is listed as a type III muscle according to the criteria set forth by Mathes and Nahai [4]. The vascular territories of the superior and inferior deep epigastric system have already been described in detail [5]. The present series confirms the utility of this flap and the broad spectrum of its application. The muscle is generally based on superior epigastric artery and its associated venous drainage system; this pedicle provides a superior arc of rotation to the chest wall. The flap includes the skin lying directly over the muscle and transverse extensions across the inferior abdomen [1]. This flap fulfills the primary goal in breast and chest wall reconstructions where it achieves adequate soft tissue coverage up to the apex of the axilla, projecting the symmetry of the breast in an aesthetically pleasing manner and has the added benefit of an incidental aesthetic abdominoplasty. Many patients in this series were satisfied with their reconstructed breasts which they felt improved their quality of life and reduced psychiatric morbidity of mastectomy.

However, the rectus abdominis muscle has another blood supply based on the inferior epigastric artery and vein [5] and thus, also has a useful inferior arc of rotation. The fact that skin can be taken transversely across the midline of the upper abdomen allows movement of a large segment of skin with rectus muscle to the groin or lower down the thigh. This confirms the observation of Marc et al [6] that this type of flap is easy, simple, speedy, safe, and above all else, successful.

The inferior-based rectus myocutaneous flap has performed well in the patient who required penile as well as urethral reconstruction in a one-stage procedure. This experience was published earlier [7].

In certain areas where bulk was not needed, especially in obese patients, we were prepared to use free muscle transfer using the microvascular technique with application of split skin graft over it. The rectus muscle free flap is ideal for medium-size defects over the lower leg and heel. The muscle is flat and long with good caliber vessels. Bradly et al [8] used this with various reconstructive problems. The main indication in our series was in the region of lower leg and feet with minimal complication of partial necrosis. The main disadvantage of free muscle transfer is the length of the surgical procedure. The surgical time in our series ranged between seven to eight hours, while Bradly et al [8] and Taylor et al [9] took only four hours. They apparently had more experience and had employed a team approach. We hope to achieve reduction of surgical time in the future.

This form of myocutaneous rectus flap, however, is not without complication, particularly if certain clinical and technical details are neglected. In our series, complications consisted of partial necrosis, subcutaneous small tumor-like fat hardness and a donor site seroma in one patient.

We noted that partial skin necrosis occurs at the lateral half of contralateral skin of superior pedicle rectus abdominis myocutaneous flap (zone 4) which was shown by Schaflan and Dinner [10] to have an unreliable blood supply. This complication occurred early in our series. When zone 4 was discarded as a routine, no more flap necrosis was seen. Clyde et al [11] advocated the use of the double pedicle to ensure greater safety. We feel this increases the risk of abdominal herniation and infection. We disagree with the authors who reported significant risk of hernia ranging from 1% to 43% [12,13]. None of our patients developed true abdominal wall herniation; only one patient developed abdominal wall weakness.

Conclusion

In our opinion, the following points must be borne in mind while transferring this flap in order to decrease the incidence of postoperative hernia, thus avoiding the need for artificial mesh: 1. The anterior rectus sheath should not be removed below the arcurate line; 2. The anterior rectus sheath repair should be tension free which can be achieved by simple approximation if a fringe of anterior rectus sheath is retained medially and laterally without leaving the lateral portion of the muscle [12] as these lateral parts of the muscle are consequently denervated [14]; and 3. We do not advise usage of double-pedicle transverse rectus abdominis as recommended by Clyde et al [11].

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BACTERIAL MENINGITIS AND HEARING IMPAIRMENT: A PROSPECTIVE STUDY

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تهدف هذه الدراسة إلى تباين معدل وقوع الصمم ونمطه في أعقاب التهاب السحايا. أجريت دراسة استطلاعية على ٦٨ مصاب بالتهاب السحايا. جرى تقييم السمع لدى المرضى بعد المرض الحاد مباشرة ثم بصفة دورية على مدى سنتين. بلغت نسبة وقوع الصمم الأولي الحسي العصبي والتوصيلي ٢٦,٤٪ و ٢٠,٦٪ على التوالي. عانى مريضان من صمم مختلط. لم نعثر على نمط مطّرد لتخطيط السمعٍ في حالات الصمم الحسي العصبي. أظهر تقييم السمع المتعاقب تعاقبًا تامًا في جميع حالات الصمم التوصيلي وتحسنًا ضئيلاً فقط في النغمات المنخفضة لدى واحد من المصابين بصمم حسي عصبي. لم تحدث حالات ظهور متأخر للصمم الحسي العصبي.

The purpose of this study is to demonstrate the incidence and the pattern of post-meningitis hearing impairment. A prospective study of 68 meningitis patients was performed. The patients' hearing was evaluated immediately following acute illness and periodically checked for two years. The incidences of the initial sensorineural and conductive deafness were 26.4% and 20.6%, respectively. Two patients (3%) suffered from mixed deafness. No consistent audiometric pattern was found in the cases of sensorineural hearing loss. Serial hearing evaluations demonstrated complete recovery of all cases of conductive hearing loss with only a slight improvement in the low tones noted in one patient with sensorineural hearing loss. No late development of sensorineural loss has occurred.

Meningitis is a leading cause of acquired sensorineural hearing loss in infancy and childhood [1]. Several studies of school-age children have shown that bacterial meningitis is the cause of 8% to 24% of all cases of severe deafness [2].

The exact incidence of sensorineural hearing impairment as a sequele of meningitis has not been established. The published studies indicate that approximately 5% to 30% of patients with meningitis develop significant hearing impairment [3].

This report concerns the assessment of hearing in a relatively long-term prospective study of the survivors of acute meningitis.

Material and Methods

Sixty-eight infants and children between two months and ten years of age treated for meningitis at Sulaimania Children's Hospital and King Khalid University Hospital, Riyadh, were entered into the study. At the time of admission, complete histories of all patients were obtained and physical examinations performed. Clinical and laboratory studies were carried out during the acute illness. The patients were treated with ampicillin, chloramphenicol or cefuroxine according to the causative organism and/or the results of the cerebrospinal fluid culture and sensitivity.

At, or prior to hospital discharge, the patients were subjected to otologic and audiologic evaluations. The protocol called for repeating the procedure every three months for a period of two years. The hearing evaluation was performed by pure tone audiometry or brain stem auditory evoked potential (BAEP) depending on the age of the patient. In addition, impedence tympanometry

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was performed on all the patients to assess middle ear function. Consents from the parents were obtained after explaining the purpose and procedures of the study.

Results

The number of acute meningitis patients entered into the study was 68; 44 (64.7%) were males and 24 (35.3%) were females. The age distribution of the patients is shown in Table 1. *Haemophilus influenzae* accounted for 40 cases (64%), *Streptococcus pneumoniae* for 12 (17.7%), *Neisseria meningitidis* nine cases (13.2%), and *Beta haemolytic streptococcus* for one case (1.5%). In six patients (8.8%), no organism was identified; however, these patients all had symptoms and signs of meningitis and cerebrospinal fluid pleocytosis with a predominance of polymorphonuclear leukocytes. The histories of children obtained on admission showed that none had a hearing problem prior to the acute illness. On hospital discharge, 16 patients (23.2%) were judged clinically to have middle ear effusion and the diagnosis was confirmed by impedence tympanometry measurement. The results of hearing assessment prior to hospital discharge of all patients are shown in Table 2. All the cases of conductive and mixed hearing impairment were bilateral. On the other hand, sensorineural hearing loss was bilateral in 24 patients (70%) including the two patients with mixed deafness; while being unilateral in six patients (30%). No consistent audiometric pattern was observed among the cases of sensorineural impairment.

TABLE 1. *The age distribution of the patients.*

Age	No. of patients	Percentage
<– 2 months	4	5.9
2– 12 "	31	45.6
13– 24 "	11	16.2
25– 48 "	12	17.6
49– 72 "	3	4.4
73–120 "	7	10.3
Total	68	100.0

TABLE 2. *Results of the hearing assessment of post-meningitis patients prior to the hospital discharge.*

Hearing Assessment	No. of patients	Percentage
Normal hearing	34	50.0
Conductive hearing loss	14	20.6
Partial S.N.H.L.	17	25.0
Mixed hearing loss	2	3.0
Complete hearing loss	1	1.4
Total	68	100.0

Within three to six months, follow-up serial hearing evaluations showed recovery of all the cases with conductive hearing loss which was due to resolution of the middle ear effusion. Of the sensorienural hearing loss cases, only one showed some improvement in the evaluation performed three months following initial assessment. Improvement was 15 to 25 db occurring bilaterally in the low tones (500–2,000 Hz). No cases of delayed hearing impairment occurred in the series. All patients with hearing impairment were followed up for a minimum of two years, and only six patients of the normal hearing children have not completed the designated period.

Discussion

The number of patients in this study is limited. Nevertheless, this shows that sensorineural hearing loss occurred in 29.4% among 68 survivors of acute septic meningitis. Other reports indicated that this incidence varied from 5% to 35% [2]. Dodge et al, believed that this wide range in the reported incidence of deafness complicating meningitis in various series is probably explained, in part, by the selection of patients, especially age distribution and percentage of cases caused by particular organisms [3]. Nadol stated that the higher figure may be closer to the actual incidence because of the difficulties in detecting hearing loss, even severe in nature, in retrospective studies especially during the acute illness; and also because partial and temporary hearing loss may go undetected even during careful follow-up [2].

Post-meningitis sensorineural hearing loss may be unilateral or bilateral and may be partial or complete. In this study, the sensorineural hearing loss was unilateral in 30% of the cases. Other investigators found 20% to 60% of the sensorineural hearing loss to be unilateral [2–5]. On the other hand, the incidence of partial hearing loss in this series was 95% of the total number suffering sensorineural impairment. This is compared with 20% to 70% previously reported [2,6]. This variability is most likely related to the efficiency in detection of partial hearing impairment [2].

Most authors found the hearing loss appearing early during the course of the disease [3]. Vienney et al, found that patients who were tested within 48 hours following admission and whose tests indicated normal hearing did not have sensorineural deficits at a later time, whereas all those who had evidence of persistent sensorineural hearing impairment at follow-up had abnormal test results earlier [7]. In general, the late appearance of sensorinueral hearing loss is very uncommon, but it has been reported to occur in up to six months following the onset of meningitis [8].

Partial or complete recovery of auditory function following meningitis has been reported [2,3]. Reports of such recovery of hearing ranged from 44% partial and 13% total recovery to none [2,6]. Recovery is more common for hearing loss at frequencies up to the range of 2,000 to 3,000 Hz; persistence of loss in the higher frequencies in the rule [3].

Brainstem auditory evoked potentials (BAEP) in this study was used to determine the type and extent of hearing loss. It is important to understand that BAEP tests high frequencies so that a selective low-frequency deafness could escape recognition. Inversely, a selective high-frequency deafness with or without any minimal influence on auditory function has been described in post-meningitis deafness. In such cases, BAEP would be unduly pessimistic [7]. Nevertheless, BAEP is important in the documentation of the early occurrence of auditory dysfunction and has a prognostic value since all patients with a normal BAEP recording at discharge were found later to have normal audiograms [7].

Transient conductive hearing loss was seen in 16 (23.5%) patients (including two patients with mixed deafness). This was attributed to middle ear effusion as judged clinically and by tympanometry. As meningitis usually starts as an upper respiratory tract infection, middle ear infection is not uncommon. In a study, Schucknecht et al, discovered 14 bones with concurrent acute otitis media in 16 temporal bones of patients who died as a result of meningitis [9].

There are several sites at which hearing may be impaired during bacterial meningitis. Bacterial labyrinthitis may occur by extension of suppurative process from the subarachnoid space through the cochlear aqueduct, bony dehiscence in the auditory canal, or along the eighth cranial nerve [2,3]. Direct nerve cell destruction in the cochlea, nerve fiber damage from acute inflammation or secondary ischemic damage (septic emboli or thrombotic occlusion due to vasculitis) may be responsible [7]. An entity of "serous" or "toxic" labyrinthitis, which is a sterile inflammatory response of the membranous labyrinth perhaps due to diffusion of toxic material via cochlear aqueduct, has also been reported [10,11]. This type of involvement has been proposed as the mechanism underlying both temporary partial and complete sensorineural hearing loss [2]. Although acute otitis media is commonly associated with meningitis, it is currently thought that involvement of the cochlea originates in the subarachnoid space rather than the middle ear [2,9].

The organism responsible for meningitis appears to be a relevant factor in the development of sensorineural hearing loss. A review of several studies showed that *Haemophilus influenza* accounted for 68% in the incidence of meningitis of which 7% had permanent hearing impairment, while *Diplococcus pneumonia* produced 13% of the meningitis, in which 24% of these patients had lasting sensorineural deafness [1].

Nadol correlated the deafness with other clinical findings in a retrospective study of 547 cases of meningitis in an attempt to identify those patients with bacterial meningitis that were at higher than average risk of developing hearing loss [2]. He found a positive correlation between the incidence of post-meningitis deafness and the interval between the first meningeal symptom and initiation of therapy. Also, the presence of other neurological complications of meningitis, CSF pleocytosis or low sugar concentration, identifies a patient to be at high risk. Dodge et al, on the other hand, in a prospective study of 185 patients, found no correlation between the number of days of illness prior to admission and the persistent sensorineural hearing loss [3]. Similarly, Munoz et al, found no differences between the patients who received appropriate antimicrobial treatment within 48 hours of symptoms and the patients who began treatment later [12].

Several retrospective studies suggested that ampicillin was responsible for the hearing loss [13]. However, more recent studies showed no differences of the incidence of post-meningitis deafness and the various forms of antimicrobial therapy [4,5,12].

At our present level of knowledge about post-meningitis deafness, no specific therapy can be recommended. Even early diagnosis and treatment of meningitis may not be enough to diminish the frequency of post-meningitis hearing loss. Prevention of meningitis is the only means of reducing this complication. Vaccination against the three most common causes of bacterial meningitis are now available and in use for children and adults. Early recognition of the hearing impairment is important in order to start appropriate speech and language therapy to facilitate optimal development. Hearing assessment should be done on all meningitis patients immediately following the acute illness with adequate follow-up.

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Case Reports

THE MANAGEMENT OF PRENATALLY DIAGNOSED SACROCOCCYGEAL TERATOMA

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Accurate prenatal sonographic diagnosis of many congenital anomalies is now possible. Fetal sacrococcygeal teratoma may be associated with a very good prognosis by utilizing prenatal diagnosis, proper intrapartum management, detailed neonatal preoperative delineation, and complete surgical excision of the tumor [1].

Sacrococcygeal teratoma (SCT) is the most common tumor of the newborn with a reported incidence of 1 in 40,000 live births [2]. Most of these cases are asymptomatic during pregnancy and diagnosed at birth. However, with the improving accuracy of ultrasonography, there have been increasingly frequent reports of antenatal diagnosis of SCT in the literature. We report on a case of SCT prenatally diagnosed and its management.

Case Report

A 37-year-old Saudi female, G9, P8, was reerred from a dispensary at 39 menstrual weeks' of gestation because of progressive distension of the abdomen. She was seen at King Abdulaziz Hospital where her vital signs were normal. General examination was normal; the abdomen was distended and tense with a fundal height of 48 cm, single fetus in longitudinal position, vertex presentation and polyhydramnios, and fetal heart were audible. Investigation included a complete blood count, liver, renal functions, and 100 gm oral glucose tolerance test which were all normal. Torch screen revealed toxoplasmosis, VDRL, cytomegalovirus and hepatitis surface antigen negative, and positive Rubella IgG. Due to the significance of polyhydramnios and a uterus larger than date, an ultrasound was performed and revealed a single intrauterine viable fetus in vertex presentation. The measurement of the biparietal diameter, femur length, and abdominal circumference correlated with the gestational age of 37 weeks. A fetal mass measuring 15 × 17 cm in diameter was seen at the buttock. It was heterogenous, mainly solid with a few small foci of calcification. A crescent-shaped peripheral fluid was seen surrounding the solid mass which was well-delineated (encapsulated mass) well separated from the buttocks. There were significant pockets of amniotic fluids measuring 8 × 8 cm. The fetal stomach, liver, kidneys, urinary bladder, spines and cranium were intact. No other anomalies could be seen. The diagnosis was consistent with sacrococcygeal teratoma (Figures 1 and 2).

An elective caesarean section was planned in view of the large size of SCT. A neonatologist and pediatric surgeon were consulted and available in the operating room. Through a midline incision, a low transverse caesarean section was performed. Three liters of bloody amniotic fluid were drained and a female infant in vertex presentation was delivered. The SCT was delivered intact with a 3 × 3 cm superficial hemangioma which was bleeding into the amniotic fluid. The apgar score was eight at one minute and ten at five minutes. The total birth weight of the infant was 3,820 gm (Figure 3). The neonate was evaluated when complete blood count, blood group, ultrasound and x-ray lateral view were performed and operated on within a few hours with complete excision of the tumor. The SCT weight was 1,060 gm and the pathology revealed a benign SCT.

On the eighth postoperative day, the mother and the neonate were discharged home in good condition. Follow-up at six months showed a normal growing infant.

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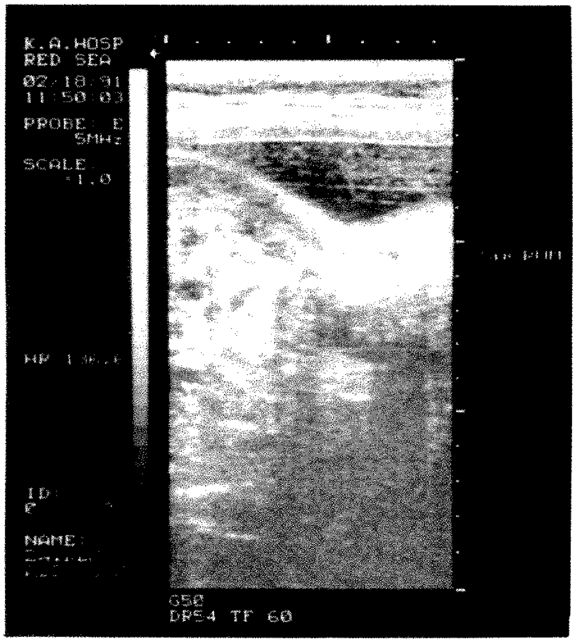

FIGURE 1. Ultrasound examination showing SCT attached to the sacrum.

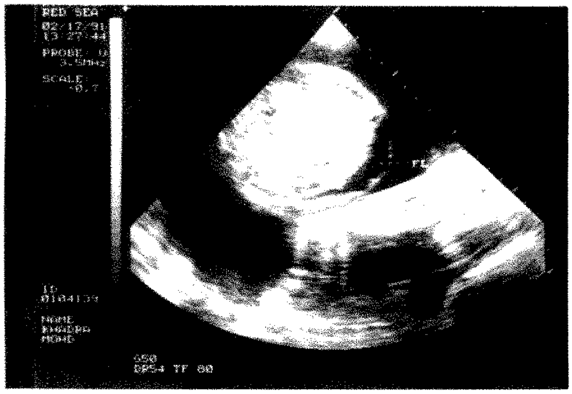

FIGURE 2. Ultrasound examination showing SCT with solid/cystic components and severe polyhydramnios.

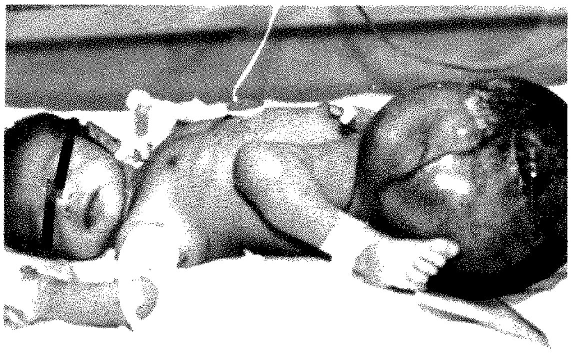

FIGURE 3. Neonate with vascular SCT.

Discussion

Sacrococcygeal teratoma is a monstrous swelling arising from totipotential cells derived from the primitive knot of the embryo and is attached to the coccyx and projects from the space between the coccyx and the rectum. Sacrococcygeal teratoma contains a wide variety of tissues derived from ectoderm, mesoderm, and endoderm i.e. all three germ layers and are usually skin-covered masses which cause distortion of the buttocks but little or no deformity of the sacrum. SCT are uncommon, occurring one in every 40,000 live births, but they represent a significant proportion of pediatric tumors and are one of the most common congenital neoplasms [2]. SCT are the most common teratomas comprising over 50% of teratomas found at birth. Those in other locations include intracranial, palatal, tongue, thyroid, mediastinal stomach, retroperitoneal umbilical cord; the gonads making up the remainder. These teratomas are the most diverse group of tumors in childhood accounting for 3% of all childhood malignancies [3]. Three-quarters of all SCT occur in females. Of those operated on neonatally, only 10% are malignant. In those operated on later than the sixth month of life, 50% may be so, suggesting malignant change in a previously benign structure. The most common types of malignancy are embryonal carcinoma and yolk-sac carcinoma [2,4].

SCT is usually an isolated occurrence; association with twinning and familial cases have been described. Patrick et al [5], reported on 26 patients with presacral teratoma associated with anorectal stenosis, sacral defects, retrorectal abscess, skin dimples and vesicoureteral reflux. Guttman et al [6] reported on three cases in one family. Characteristically, familial SCT are 100% presacral masses with a ratio of female to male of 1:1 and are firmly adherent to the rectum [6]. Rayburn et al [7], reported on a teratoma in a mother and her fetus. SCT must be differentiated from other masses presenting in the sacrococcygeal area by careful clinical and histological studies since the other lesions generally require a different therapeutic approach. The important differential diagnosis includes anterior and posterior sacral meningocele or myelomeningocele, lipoma, dermoid cyst, angioma, acute abscess, perirectal abscess, infected pilonidal cyst, chordoma, neuroblastoma, neurofibroma, hamartoma, cystic hemangioma, lymphangioma, presacral teratoma, cystic duplication of the rectum, meconium pseudocysts, myxopapillary ependymomas, ependymal rest, extraspinal glioma and ganglioneuroma [3,6,8–10].

Prenatal Diagnosis

SCT is often not diagnosed prenatally but at present, ultrasound examination of the gravid uterus may lead to prenatal detection of SCT. Thus, early prenatal diagnosis of SCT should not necessarily dictate abortion as the treatment of choice.

Chervenak et al [11], reported on three cases of SCT diagnosed prenatally, all delivered by caesarean section; one died from prematurity. Gross et al reviewed their five years' experience in ten cases of SCT with six cases diagnosed prenatally by ultrasound. Four had caesarean section and two had elective abortion, a large uterus or polyhydramnios being the indication for ultrasound examination in the majority of cases [12]. El-Qarmalawi reported on three cases of SCT prenatally diagnosed. One patient with small SCT delivered spontaneously, the second and third were stillbirths [13]. Ikeda et al reported three cases. The first was delivered vaginally and the second by caesarean section, both unsuccessfully. The third one was delivered at 35 weeks by caesarean section and survived [14].

With ultrasound, teratomas generally appear to be almost all cystic or mixed cystic/solid. The solid component is often not homogeneous in density and may contain calcifications which may be teeth or bone, and the cystic parts frequently have irregular spaces which are formed by cavities lined by neural, respiratory, gastrointestinal, or squamous epithelium. Almost all cystic or mixed teratomas have been benign whereas most solid tumors have been malignant. Calcification has been almost exclusively confined to benign tumors. In only 15% of cases is the tumor predominantly cystic [11–18]. If a fetal teratoma is suspected by ultrasound examination, a careful search for other anomalies should be performed. Anomalies, especially of the musculoskeletal, anorectal, genitourinary and nervous systems, have been reported in association with SCT. Altman et al [19], reported an 18% incidence of newborn anomalies in babies with SCT compared with 2.5% in the unselected population. They classified these tumors according to its location into Type I–totally external, Type II–almost completely external, Type III–almost completely internal, and Type IV–internal. Amniotic fluid alpha fetoprotein (AFP) and acetylcholinestrase levels may be elevated. Polyhydramnios is associated with the majority of SCT. The mechanisms by which hydramnios are produced in the SCT remain unclear [11]. Other less sensitive methods for diagnosis of SCT include abdominal x-ray [15,20], and amniography [21]. Fetuses affected by SCT may be complicated by congestive heart failure which may be diagnosed prenatally by a two-dimensional Doppler echocardiography [22]. Large SCT early in gestation may result in placentomegally, hydrops fetalis and fetal death and a pre-eclampsia-like syndrome in the mother. This chain of events may result from a high output cardiac failure in the fetus caused by arteriovenous shunting through the tumor. Anemia or hypoproteinemia following massive hemorrhage seems to be reasonable mechanisms for the development of fetal hydrops [23]. Langer et al reported the first case of intrauterine open fetal surgery for excision of SCT resulting in reversal of hydrops at 22 weeks' gestation but uterine irritability after hysterotomy resulted in labor and delivery of a non-viable premature infant [24]. The SCT varies in size from a few centimeters to a large one. The greatest dimension reported by Grosfeld and Billmire was 30 cm in diameter [3], in which a special technique during resection to control tumor bleeding as described in a large case of 1,300 gm by Lindahl may be needed [25].

The principles of management in the prenatally diagnosed SCT include accurate diagnosis, strict follow-up by serial ultrasound for the size of the tumor, and delivery in a tertiary center where facilities for immediate neonatal surgery are available. The important questions are when and how to deliver the fetus [11]. Early delivery is not recommended except when the progressive growth of the tumor causes obstruction of the gastrointestinal or urinary tract, both suggestive of malignancy and if rapid development of hydrops fetalis occurs [26]. The literature documents different modes of management: vaginal delivery [15], elective caesarean section [11], caesarean section following partial delivery because of dystocia [27], vaginal drainage of tumor followed by vaginal delivery or abdominal drainage of tumor followed by vaginal delivery [28,29] or destructive procedures [30]. While the mode of delivery has been individualized in the literature, tumor size is critical in this decision for two reasons.

If the tumor size is relatively small (5 cm) or located internally the patient may be permitted to have a vaginal delivery [12], while a large tumor may cause serious obstetric complications such as abnormal lie, dystocia and avulsion of the tumor. With large tumors, elective caesaran section is the procedure of choice [31]. Aspiration under ultrasound guidance may be attempted just prior to delivery [28] while destructive procedures should be performed only in exceptional circumstances. Occasionally, SCT is diagnosed only when dystocia supervenes [27,29,30,32–37]. This serious complication has been estimated to occur in 6% to 13% of all cases and is commonly associated with tumors larger than 10 cm. The large SCT prevents the descent of the fetus through the birth canal resulting in fetal death due to trauma or rupture of the tumor [29,30,36]. SCT may be diagnosed intrapartum if, during the second stage of labor and after delivery of the head and the thorax, the obstetrician cannot deliver the rest of the body. If the partially delivered fetus is alive, gentle traction and fundal pressure should be tried. If failed, the infant should be intubated and ventilated while the patient is prepared for laparotomy. If the tumor is solid, an assistant can push the head from below and the infant can be delivered abdominally [27]. Amputation of a solid tumor is not recommended. If the tumor is mostly cystic, aspiration can be performed at the time of caesarean section and the fetus is then delivered vaginally [28]. If the partially delivered fetus is dead, amputation of the tumor can be performed at the time of laparotomy and the infant delivered vaginally [38]. However, pregnancy and labor are often uncomplicated and the tumor is recognized only at birth or soon afterwards in 90% of cases [39]. These are relatiely small teratomas that slip through the pelvis during labor behind the fetus which usually presents cephalically.

At the time of elective caesarean section delivery for SCT in infants, a team approach is critical. A neonatologist should be present in the operating room to examine the neonate and provide immediate resuscitation and endotracheal intubation if needed. A pediatric surgeon should be consulted. In our case, accurate prenatal diagnosis by ultrasound allowed adequate preparation for elective caesarean section with a good outcome for the child. Complete surgical extirpation should be the goal in each of these tumors as this offers the best chance of cure. SCT should generally be removed in a single operation with preservation of the perineal anatomy. When excision of the coccyx (coccygectomy) is included, recurrent rates are very low. If there is intra-abdominal extension, a combined abdominal-sacral approach may be necessary [3–11]. Careful follow-up of benign lesions is mandatory. Regular monitoring of patients has been facilitated by the use of AFP as a tumor marker and has become a standard part of the follow-up [40], since malignant recurrence following initial excision has been reported. Dewan et al reported on two of 19 patients with SCT presented with late malignant recurrence after excision of the benign SCT [41]. Malone et al followed 27 patients with SCT and found 41% had some form of functional impairment [42].

Summary

On the basis of the above literature review [3,43–45], we feel it is reasonable to recommend that, except for very small tumors (< 5 cm in diameter), caesarean section affords the obstetrician maximal control, since with a larger tumor, fetal complications such as hydramnios, preterm labor, non-immune hydrops fetalis, malpresentations and dystocia are common.

Thus, with prior knowledge, adequate preparation can be made with respect to obstetric management. Appropriate surgical and pediatric care can be obtained with a good outcome anticipated in most cases.

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SYMPTOMATIC RATHKE'S CLEFT CYST

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A rare case of symptomatic Rathke's cleft cyst in a 26-year-old female is reported. The clinical and radiological features of this lesion are described with emphasis on the differential diagnosis between Rathke's cleft cyst and craniopharyngioma.

Rathke's cleft cysts present a common incidental intrasellar autopsy finding occurring in 13% to 22% of randomly examined pituitary glands [1]. These lesions rarely, however, enlarge sufficiently enough to cause compression of adjacent neural structures. Although to date, approximately 155 cases of symptomatic Rathke's cleft cysts have been reported in the pertinent literature [2]; the condition continues to be largely unknown to clinicians.

The purpose of this case report is to draw attention to this pathological entity which should be considered in the differential diagnosis of cystic lesions in the sellar area. To the best of our knowledge, this is the first case of symptomatic Rathke's cleft cyst to be reported from Saudi Arabia.

Case Report

This 26-year-old Filipino female dietitian presented to the Neurosurgical Division of the King Khalid University Hospital with a two month history of constant headaches which were associated with nausea and non-projectile vomiting. There were no visual disturbances and apart from oligomenorrhea since puberty, her past medical history was unremarkable.

Examination

The patient was short in stature (height 140 cm and weighed 37.5 kg). Skin and hair distribution were normal. Neurological status of the patient was normal except for a bi-temporal hemianopia.

The plain x-ray of the skull revealed erosion of the dorsum sellae with no sellar abnormality. Cranial computerized tomographic (CT) scan showed a large low density lesion measuring 30×39 mm with faint ring enhancement filling the entire suprasellar space with compression of the third ventricle (Figure 1). The magnetic resonance imaging (MRI) demonstrated the lesion extending into the sella and elevating the floor of the third ventricle. The lesion was hyperintense on both T1 and T2 weighted images except for a small nidus which could have represented a solid component of the lesion. The vertebral angiography disclosed marked dorsal displacement of the distal end of the basilar artery.

The basal secretion of the following hormones was normal: T3, T4, TSH, cortisol, prolactin, LH, FSH, and growth hormone. The pituitary dynamic tests after injection of insulin, TRH, and GnRH revealed inadequate GH and FSH responses.

Operation

The patient underwent a right frontotemporal craniotomy. A thin-walled, brown-greenish cyst was encountered. The right optic nerve was stretched over the cyst wall and the right carotid artery was displaced laterally. The cyst was punctured and 35 cc of milky greenish fluid was aspirated. The inferior part of the cyst wall was excised leaving the superior part, which was firmly attached to the floor of the third ventricle, unremoved.

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Postoperative Course

The patient recovered well but developed transient diabetes insipidus which was controlled with vasopressin. Two years following surgery, the patient remains asymptomatic except for irregular menstruations. The basal secretion of the pituitary hormones is normal and her visual fields have normalized. The cranial CT scan was normal (Figure 2).

Pathological Examination

The histopathological examination of the excised cyst wall showed loosely arranged fibrous connective tissue covered on one side by a layer of ciliated cuboidal to columnar epithelium in some areas and flattened cells in others (Figure 3). A few single goblet cells that showed strong staining by alcian blue were scattered among the cuboidal epithelium. No areas of hemorrhage or hemosiderin deposits were observed.

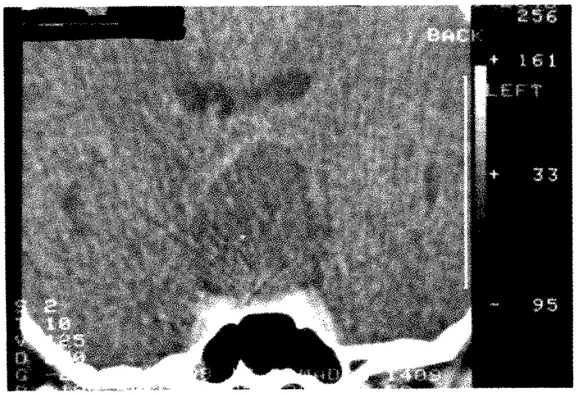

FIGURE 1: Preoperative, post-contrast, coronal CT-scan of the sellar region showing a large low density mass with a faint, capsular enhancement, measuring 30×39 mm and completely occluding the third ventricle.

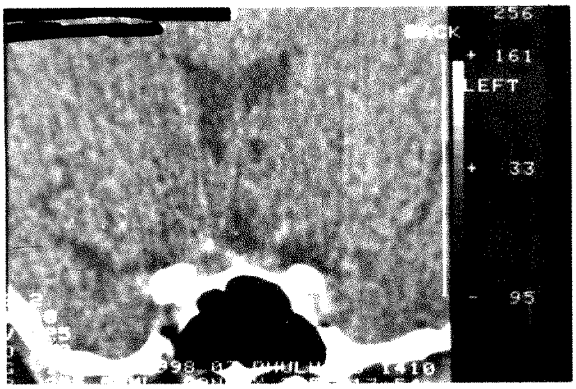

FIGURE 2: Postoperative, post-contrast CT-scan demonstrating total removal of the cyst with normal visualization of suprasellar cistern and third ventricle.

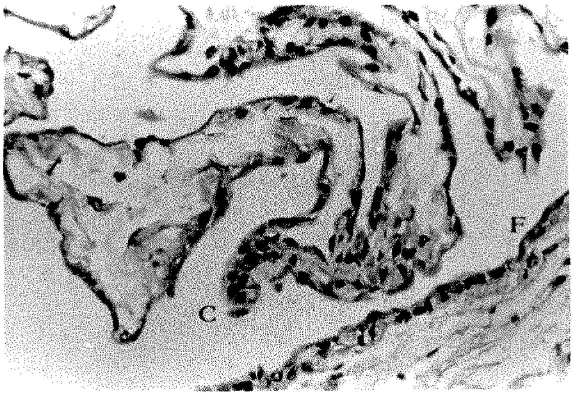

FIGURE 3: Photomicrograph of the cyst wall showing areas of flattened (F) and cuboidal (C) epithelium (H&E, ×120).

Discussion

The exact origin of Rathke's cleft cyst is unknown. The most popular hypothesis is that it derives from remnants of the Rathke's pouch, a superior diverticulum of the stomodeum [3–5]. Alternatively, it has been suggested that Rathke's cleft cyst is a neuroepithelial derivative [6] or develops by reverse metaplasia from anterior pituitary cells [7]. Based on the demonstration of amyloid stroma in a Rathke's cleft cyst, a neural crest origin was also proposed [8]. On the other hand, electron microscopic evidence of a coating material surrounding cells with microvilli raised the possibility that Rathke's cleft cyst could present endodermal inclusions from the upper respiratory tract [5,9].

The majority of Rathke's cleft cysts remain asymptomatic throughout life. The reason why only a small number of cysts progressively enlarge until they become symptomatic remains obscure. Mucous secretion and hemorrhage into the cyst and inflammatory reactions (septic or aseptic) in the cyst wall may contribute to cyst enlargement [5,10,11].

Most of the symptomatic Rathke's cleft cysts present between the third and sixth decades of life. Females are doubly more affected than males [2]. The clinical symptoms produced by Rathke's cleft cyst are almost uniformly a result of compression of the pituitary and/or suprasellar structures. Decreased visual acuity, visual field defects, hypopituitarism, diabetes insipidus, and headaches are the main manifestations [2,3,5].

Occasionally, Rathke's cleft cyst may present similar to a craniopharyngioma with aseptic meningitis with pyrexia and impaired consciousness [12,13]. Obstructive hydrocephalus and bacterial abscess formation in a Rathke's cleft cyst have also been reported in a few cases [14,15].

The diagnosis of Rathke's cleft cyst may be suspected in cases with a CT scan showing low density intra- and suprasellar lesions with no calcification and either no enhancement or a ring-like enhancement following injection of contrast material [10,16]. A Rathke's cleft cyst rarely presents with higher or mixed attenuation values with or without calcification [2]. The MRI features of Rathke's cleft cysts are also unspecific and depend on the content of the cyst [11,16]. Cysts containing CSF-like fluid appear hypointense on the T1-weighted image (T1-WI) and hyperintense on the T2-weighted image (T2-WI). Hyperintensity on both T1-WI and T2-WI, as in our patient, has been considered suggestive of the presence of blood [11]. Nevertheless, the histopathological examination of the cyst wall in our case did not reveal any evidence of old or recent bleeding into the cyst.

Rathke's cleft cyst is typically lined by ciliated cuboidal or columnar epithelium and, therefore, is quite distinct from craniopharyngioma which consists of squamous epithelium [3–6,17]. However, cysts with mixed histological features of Rathke's cleft cysts and craniopharyngioma have been described [5,9,12,18]. Such observations suggest that Rathke's cleft cysts and craniopharyngioma may be closely related and share a common cellular origin. However, some authors attributed the presence of squamous epithelium in some Rathke's cleft cysts to metaplasia from the columnar epithelium [19].

Rathke's cleft cyst is considered to be a more benign lesion than craniopharyngioma. While complete removal or partial resection followed by radiotherapy presents standard treatment of craniopharyngioma, Rathke's cleft cysts may be managed adequately by simple aspiration of the fluid [4,20,21]. However, to avoid recurrence [5,22] evacuation of the cyst and liberal resection of the cyst wall are recommended [23]. Intrasellar cysts with or without suprasellar extension are best approached transsphenoidally while cysts which are mainly suprasellar such as our case usually require a transcranial approach [2]. Although postoperative radiotherapy is generally considered to be unnecessary, it has been employed in a few cases [12].

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CHRONIC SUBDURAL HEMATOMA PRESENTING AS MULTIPLE SCALP SWELLINGS: REPORT OF AN UNUSUAL CASE

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The case of a child who had multiple progressively enlarging "scalp" swellings associated with rapidly rising intracranial pressure following a head injury is reported. Unusual computerized tomographic (CT) scan findings of this atypical chronic subdural hematoma/hygroma and its surgical management are discussed. The relationship between chronic subdural hematoma and subdural hygroma and their etiopathogenesis are reviewed.

Chronic subdural hematoma in the infant represents one of the most common and the least understood entities in pediatric traumatology [1].

Etiopathogenesis, natural history and management of chronic subdural hematoma, hygroma and "growing skull fractures" remains controversial. Our case represents a complicated clinical condition with atypical features of all these three entities. Rapid growth of subdural fluid collection and skull fractures led to a rapidly enlarging head with extracranial herniations of subdural space through gaping skull fractures. Massive extracerebral fluid collection caused a rapid increase of intracranial pressure (ICP) with gross cerebral damage and atrophy secondary to pressure from without (as opposed to pressure from within by hydrocephalus). Rapid progression and growth of subdural collection with a malignant course in our case represents one end of a spectrum, of which the other extreme is marked by a benign course and spontaneous resolution. Further studies are needed to elucidate the mechanism(s) responsible for the growth or resolution of these intracranial - extracerebral fluid collections.

Case Report

A 17-month-old female was admitted because of progressive enlargement of the head over a three to four month period followed by the appearance of multiple "scalp swellings" two weeks later. These swellings enlarged progressively and became very tense. On enquiry, the mother gave a history of a fall from height and head injury with a skull fracture one month prior to any noticeable swellings on the head. The head injury was treated at a village dispensary without hospitalization, although difficulty in walking was noticed soon after the head injury. Three weeks prior to admission, the child developed squint, visual deterioration, slow cerebration and inability to stand, walk or talk. The past medical history was unremarkable, the child having normal head, intelligence, and landmarks prior to head injury.

Physical examination revealed an obtunded child with a moderately large head (circumference 53 cm) studded with multiple tense, spherical swellings of varying sizes (Figure 1). These swellings were located bilaterally, occupying frontal, occipitoparietal and temporal regions as well as the vertex. Prominent scalp veins indicated raised ICP. An ugly, linear scar indicative of traditional bedouin treatment of "cautery" (touching the skin with red-hot iron) was noticeable on the scalp (Figure 1). Skull palpation revealed multiple asymmetrical, gaping "fractures". Fundi showed bilateral papilledema. Neurological examination

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revealed spasticity of all four limbs with pyramidal signs, bilaterally upgoing plantars and sixth nerve paresis.

Skull x-rays showed multiple gaping "fractures". Computed tomographic (CT) scan (Figure 2) showed extensive, bilateral subdural fluid collection. This hypodense extracerebral collection extended extracranially into the tense scalp swellings through the bony gaps (Figure 2). The brain was small, atrophic and shifted to the right side.

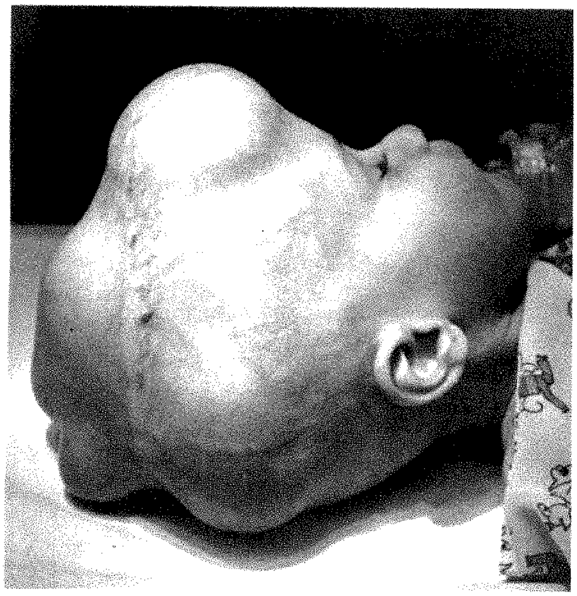

FIGURE 1. Preoperative photograph showing multiple tense swellings, engorged scalp veins and the "cautery" mark.

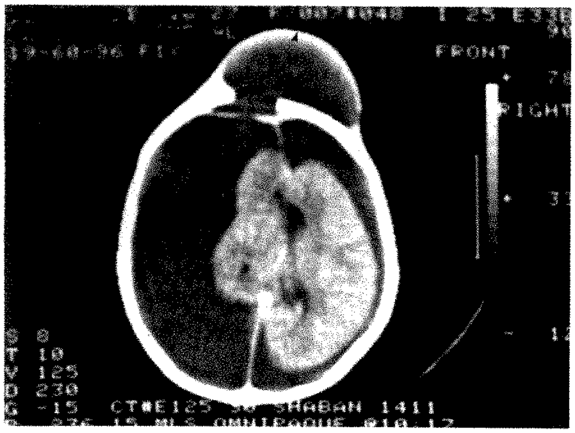

FIGURE 2. CT scan of head showing: extensive bilateral subdural fluid collection, herniation of subdural collection into tense scalp swellings through the bony gaps (arrow) and remarkably atrophic and shifted brain with normal ventricles.

Hospital Course and Management

Shortly after admission to the neurosurgery ward, the child started repeated projectile vomiting, became opisthotonic and drowsy. 80 ml of golden-colored fluid was aspirated from one of the scalp swellings as an emergency measure to relieve the dangerously elevated intracranial pressure. This resulted in dramatic relief with improvement of conscious level. Protein content of the fluid was 2 gm/L. A left-sided subdural-peritoneal shunt was carried out the following morning to drain chronic subdural collection. A low pressure pudenz shunt was used. During surgery, a small left-sided craniectomy revealed thickened and congested dura with an attempt at membrane formation. Xanthochromic fluid under enormous pressure escaped through a small dural incision. Figure 3 shows the subdural-peritoneal shunt in position with "flattening" of the head swellings.

Postoperatively, the child improved dramatically. Vomiting, papilledema and to some extent, limb spasticity resolved. Multiple, tense cranial swellings disappeared and were replaced by depressed areas.

One month later, follow-up examination revealed an asymptomatic and alert child, now beginning to take a few steps and utter a few words.

Discussion

Complex, borderline cases with features of many poorly understood conditions such as chronic subdural hematoma (SDH), hygroma and

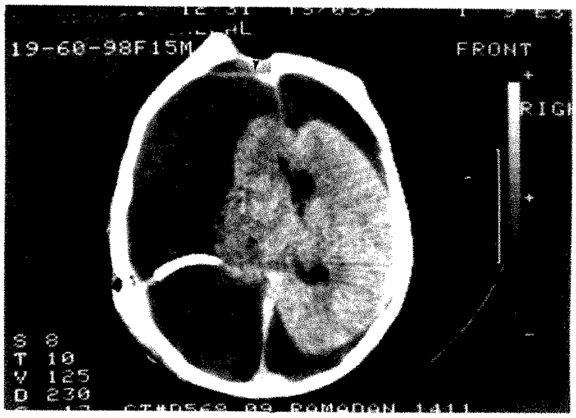

FIGURE 3. CT scan of brain with subdural-peritoneal shunt in position. Note "flattening" of scalp swelling (arrow).

growing fractures emphasizes the multifactorial, spectrum-like nature of these entities and sheds some light on their etiopathogenesis.

Subdural hygromas are defined as clear, xanthochromic, or blood-tinged fluid collection located within the subdural space following head injury [2]. The borderline between chronic SDH and hygroma is very indistinct in children.

Pathogenesis of hygroma, like SDH, remains unclear. Most authors [3,4] suggest that a tear in the arachnoid allows the escape of CSF into the subdural space. The hygroma enlarges because CSF becomes trapped in the subdural space as a result of a flap-valve effect [5]. Others [6] suggest that hygromas originate as a result of effusions into the subdural space from injured capillaries in the underlying brain. The fact that the protein content of the hygroma fluid is often markedly higher than that of CSF [7] would support this theory. Presence of membrane often suggests a chronic subdural hematoma rather than a hygroma, although membrane formation surrounding hygroma has been reported [4,8]. It is presumed that subdural hygroma has a milder and more benign clinical course and resolves spontaneously [7]. This we believe, is only one end of the spectrum. At the other end of the spectrum are the cases where accumulation of fluid may occur so rapidly and become so extensive in volume as to cause acute increase in intracranial pressure with splitting of fractures, sutures, and bulgings of anterior fontanelle; as occurred in our case. On CT scan, both chronic SDH and hygroma appear as hypodense extracerebral collections. Thus, on etiopathological, clinical and radiological grounds a subdural hygroma is indistinguishable from chronic SDH [2,9]. Subdural hygroma, particularly in infants and children, should therefore be considered to be a variant of chronic SDH rather than a separate clinical entity. This would ease the classification of complex cases such as the one presented here.

Our case had the additional complicating factor of multiple "growing" skull fractures, but the features were not typical. Linear or non-linear skull fractures in infants that enlarge with time are termed growing skull fractures [10]. Initial trauma in our case fractured the skull and probably tore the dura. Over the ensuing weeks, extensive collection of subdural fluid and acute increase in intracranial pressure led to herniation of the subdural space out through the fracture sites with an increase in the size of fractures and swellings of the overlying scalp. The classical features of growing skull fracture (Meningocele spuria), namely incarceration or impaction of torn dural fragments and herniated brain through the fracture site and later development of a tense porencephalic cyst [1,10] were absent in our case. The relationship between skull fracture, porencephalic cyst and subdural fluid collection has previously been pointed out [9]. Management of subdural fluid collections has been a subject of controversy [2]. A number of "treatments" have been proposed: corticosteroids, twist drill evacuation, burr-holes, craniotomy with excision of membranes or even the lowering of the superior sagittal sinus to address the presumed cause of "hanging veins" [1]. All appear to work at times. On the other hand, recurrence of subdural collections is not uncommon. It is well known that these collections may disappear after burr-hole drainage, but may also persist despite continuous drainage with subdural-atrial or subdural-peritoneal shunts [11]. For a treatment to succeed, it must address the major causal mechanism(s). Thus, corticosteroids may inhibit protein permeation from capillary walls [12], drainage and washing of fibrinolytic enzymes may be required when recurrent hemorrhage is the main factor [13], and a permanent internalized shunt will be needed to address a persisting subarachnoid-subdural fistula with a flap valve mechanism. Surgery should be advised when these collections lead to increased intracranial pressure with mass effect and displaced midline structures; in bilateral hygromas with secondary brain atrophy and in enlarging hygromas despite clinical stability.

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SPONTANEOUS PERFORATION OF THE EXTRAHEPATIC BILE DUCTS–PATHOGENESIS AND MANAGEMENT: CASE REPORT AND REVIEW OF THE LITERATURE

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Spontaneous perforation of the extrahepatic bile ducts is an uncommon condition which occurs almost exclusively during infancy. In 1932 this condition was first reported by Dijkstra [1], who described a small perforation at the junction of the cystic and common bile ducts in an autopsy of a three-month-old infant who died of jaundice and progressive abdominal distention. Since then there have been sporadic case reports from different parts of the world describing this condition [2–4]. Occasionally the presentation of spontaneous perforation of the extrahepatic bile ducts is classic, but in the majority the diagnosis is made intraoperatively.

This is a case report of spontaneous perforation of the extrahepatic bile ducts and review of the literature, outlining the possible etiological factors and methods of treatment.

Case Report

A four-year-old female was admitted to the hospital because of abdominal pain and vomiting of four days' duration. On examination she looked ill, was afebrile and not jaundiced. There was a right-sided tenderness with guarding and rigidity. Bowel sounds were hypoactive. Laboratory investigations showed leukocytosis of 16 × 10^9/L with 73% polymorphs, 6% bands, 16% lymphocytes and 5% monocytes. Hemoglobin was 11.2 g/dl. Her urine analysis and electrolytes were normal.

She was diagnosed as having peritonitis secondary to a perforated appendix. Under general anesthesia, there was a mass in the right lumbar region. Through a right transverse incision at the level of the umbilicus, the peritoneal cavity was opened. There was bile peritonitis and the appendix was found to be normal. There were loculi of bile-stained fluid and further exploration revealed a normal gallbladder and a bile leak at the porta hepatis. Intraoperative cholangiography revealed leak in the common hepatic duct posteriorly above the junction of the cystic and common hepatic ducts (Figure 1). There was also a constant filling defect at the lower end of the common bile duct suggestive of a stone (Figure 1) and the junction of the pancreatic and common bile duct was found to be high (Figure 2), indicating an anomalous arrangement of the pancreaticobiliary system with a long common channel. Cholecystectomy and exploration of the common bile duct were

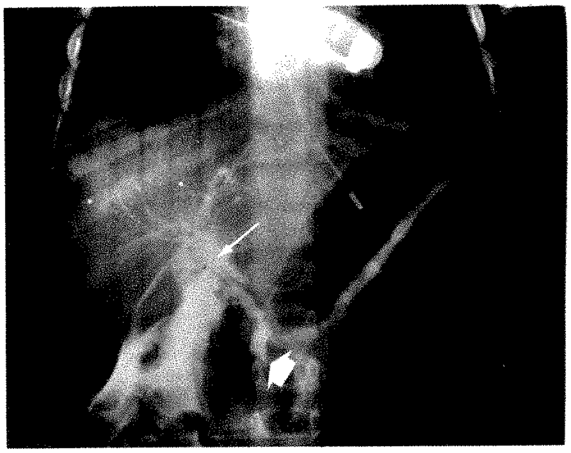

FIGURE 1. Intraoperative cholangiogram demonstrating leakage from the common hepatic duct; (thin arrow) showing a filling defect in the lower part of the common bile duct, (wide arrow) showing common bile duct stone.

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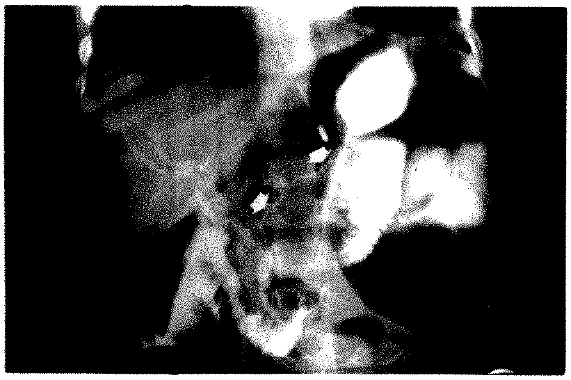

FIGURE 2. T-tube cholangiogram demonstrating an anomalous arrangement of the pancreaticobiliary (arrows) system with a long common channel.

done and after several attempts it was possible to pass a catheter down into the duodenum. A T-tube was inserted and a drain was left in the subhepatic area. Postoperatively, the patient did well and was discharged home on the 14th postoperative day. The T-tube cholangiogram was normal and amylase level from the T-tube on the second and 13th postoperative days showed high levels of 60,640 and 59,000 units respectively, while serum amylase and liver function tests were normal. Seven weeks following her discharge, she was readmitted with mild abdominal pain and vomiting of one days' duration. An intravenous cholangiogram was normal. The patient improved and was discharged home on the second day. She is now 20-months postoperative and free of symptoms.

Discussion

Spontaneous perforation of the extrahepatic bile ducts is an uncommon condition seen during infancy, mostly between the first and third months of life [5]. Our patient was four-years-old and Okhawa et al [6] reported three cases; 11 months, 37 months and 53 months of age. These four cases are outside the common age group and all had a common anomalous arrangement of the pancreaticobiliary system with a long common channel as a possible cause for perforation. The youngest patient reported was one-week-old [7], but there are reports in the literature of spontaneous perforation occurring in adults [8,9]. The most common site of perforation is in the common bile duct near the entrance of the cystic duct, but there are reports, including ours, of spontaneous perforation of the common hepatic duct [10,11].

The exact etiology of spontaneous perforation of the extrahepatic bile ducts remains unknown. Infection in the form of portal bacteremia localizing in the venous plexus surrounding the bile ducts was considered as the possible etiology, but this was later discounted [7]. Distal common bile duct obstruction which was found in some reported cases [3,11,12], including ours in the form of obstructing stone or sludge, has been considered an etiological factor. We, like others, feel [12,13], especially in the absence of common bile duct dilatation, that this is a secondary phenomenon due to bile stagnation in the temporarily dysfunctional common bile duct distal to the perforation rather than the cause of perforation. In these cases, operative cholangiograms may be deceptive suggesting distal common bile duct obstruction as occurred in our case. This may lead to unnecessary procedures, especially as this has been shown to disappear by itself after healing of the perforation [4]. The most common site of perforation is the junction of the cystic and common bile duct. This site is particularly vulnerable to errors in development suggesting possible localized embryological weakness in the wall of the duct that perforates after a certain intraductal pressure is rendered. Such a concept has also been advanced for the pathogenesis of choledochal cysts [14,15]. In 1969, Babbit [16] demonstrated an anomalous junction between the pancreatic and biliary duct system (AJPBDS) causing retrograde reflux of pancreatic juice into the common bile duct because of the lack of sphincteric mechanism. This reflux is further enhanced by the fact that pancreatic ductal pressure is higher than that found in the common bile duct. This anomaly has been considered an important factor in the pathogenesis of choledochal cyst, perforation of the extrahepatic bile ducts and pancreatitis. We feel the presence of an anomalous junction of the pancreaticobiliary tract in our patient has contributed to the pathogenesis of spontaneous perforation of the bile duct.

Although one case of a successful outcome after non-operative management has been reported [17], the treatment of spontaneous perforation of the bile duct is surgical exploration as noninvasive treatment is usually fatal [1,3,11,12]. Several methods of surgical treatment for this condition have been described. Case Reports have been published describing these methods but controversy exists as to the optimum form of surgical treatment. A review of the literature has revealed 82 cases of spontaneous perforation of the extrahepatic bile ducts. Of these, 76 had surgical treatment and 66 survived. Of the different methods described, simple drainage is the most favored procedure and most of the time it is all that is usually required and results in spontaneous closure and subsequent cure. Although widely advocated, when compared with other methods namely T-tube drainage, it has been reported to have increased mortality and morbidity with increased hospital stay [3,9,12,18]. The youngest patient treated with T-tube drainage was one-week-old [7]. All of those treated with this method have survived. T-tube drainage also provides a means to visualize the patency of the bile ducts postoperatively. We suggest that this form of therapy, rather than simple drainage be the treatment of choice in such patients as other complicated procedures [3,12] are unnecessary and have been associated with a high morbidity and mortality rate.

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UPPER GASTROINTESTINAL TRACT LESIONS IN HENOCH-SCHONLEIN SYNDROME

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Henoch-Schonlein syndrome is a disorder causing cutaneous and systemic small vessel vasculitis with characteristic clinical signs. Gastrointestinal manifestion occurs in 35% to 70% of cases [1,2]. The most common pathological abnormality in the gastrointestinal tract is submucosal and mural infiltration of bowel by edema or blood. Microscopically it shows changes of vasculitis with endothelial proliferation and thrombosis of small arterioles. Immunofluorescent studies may show granular deposits of immunoglobulin A and complement components (C3) in the bowel vessel walls [3,4] similar to those observed in the skin and kidneys.

Barium studies of the upper or lower gastrointestinal tract may show findings suggestive of Henoch-Schonlein syndrome [1,5].

Characteristic endoscopic lesions resembling those of the skin have been reported in the colon [6] while those reported in the upper gastrointestinal tract include duodenitis [6], multiple ulcerations and thickening of mucosal folds [3] or ulcerated gastritis [4].

In this communication we report a patient in whom gastroscopy showed typical lesions in the stomach and duodenum resembling those of the skin.

Case Report

A 19-year-old Saudi male presented with a two week history of upper abdominal pain, vomiting and a one week history of skin rash. There was no fever, joint pains or urinary symptoms. There was no history of recent immunization or drug therapy.

There was bilateral symmetrical maculopapular purpuric skin rash over the forearms, thighs, buttocks, and legs. Blood pressure was 150/100. There was epigastric tenderness. Cardiovascular and respiratory system examination was normal There was mild epigastric tenderness and examination of the joints was normal. A clinical diagnosis of Henoch-Schonlein syndrome was made.

Relevant laboratory investigations showed leukocytosis and erythrocyte sedimentation rate (ESR) of 30 mm/hr. Hemoglobin, platelets and coagulation profile were normal. Liver function tests showed an elevated alkaline phosphatase, low total serum proteins and albumin. Serum amylase, urea and electrolytes were normal. An autoimmune screen was negative. Serum IgE, IgM, IgA were elevated. Serum complement C3 and C4 were normal. Stool examination was positive for occult blood. Urinalysis showed mild proteinuria. Renal biopsy showed focal mesangioproliferative glomerulonephritis with mesangial immune complex (IgA) deposition. A skin biopsy showed leukocytoblastic vasculitis. A chest x-ray and ultrasound of the upper abdomen were normal. Small bowel enema showed mucosal fold thickening and marked edema of the ileum (thumb printing).

Because of abdominal pain, vomiting and positive occult blood in the stool, gastroscopy was performed. This showed multiple petechial and purpuric lesions 2 to 3 cm wide in the antrum, fundus, and the first and second part of the duodenum (Figure 1). These lesions resembled a skin rash. Endoscopic biopsies from the duodenum and stomach showed inflammatory changes with

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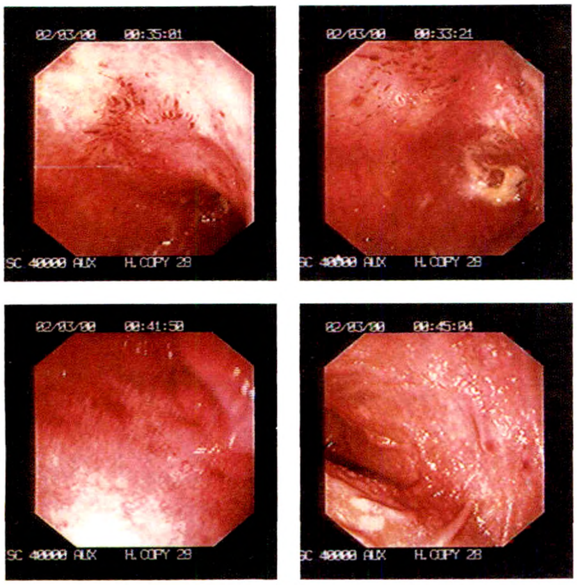

FIGURE 1. Gastroscopy showing lesions resembling purpuric skin rash in stomach (above) and duodenum (below).

eosinophilic and plasma cell infiltrate in the lamina propria.

He was treated for hypertension with nifedipine. A tapering dose of prednisolone and ranitidine was also given. He was discharged after ten days in good condition. A follow-up gastroscopy after one month was completely normal. He was followed in the outpatient clinic for one year, during which period he was asymptomatic with a normal blood pressure.

Discussion

Gastrointestinal manifestations occur in up to 70% of patients with Henoch-Schonlein purpura [1,2,6] and these may precede the development of the characteristic skin rash, as in our patient. Abdominal pain, blood loss and other gastrointestinal symptoms occurred in 34 of 77 patients with Henoch-Schonlein purpura as studied by Cream et al [2]. Gastrointestinal bleeding may result from intramural hemorrhage or mucosal ulceration [7,8]. Surgical complications may occur and about 10% of patients may undergo laparotomy for bleeding, perforation, infarction, intussusception and obstruction [9–14].

Our patient presented with abdominal pain and had minor gastrointestinal bleeding, as seen during gastroscopy, and had a positive occult blood test in stool. The gastroscopic findings showed lesions (Figure 1) resembling those of the skin. Cappell and Qupta [6] recently reported colonic lesions resembling those of the skin in two patients who had Hemoccult positive stool.

Bowel inflammation, ulceration or edema may cause protein-losing enteropathy [2] as in this patient who had a low serum protein which improved after treatment.

Beauchant et al [3] and Touchard et al [4] reported endoscopic and/or radiological or histological evidence of ulcerated gastritis, duodenojejunitis or ileitis in five of their patients. Immunofluorescent studies on fresh biopsies from these patients showed heavy granular deposits of IgA and C3.

Barium studies in Henoch-Schonlein purpura may be normal or show different lesions as mucosal edema and thickened mucosal folds, as observed in this patient [1,5,6].

In Henoch-Schonlein purpura, upper or lower gastrointestinal tract endoscopy may be helpful in diagnosis especially if typical lesions resembling those of the skin can be seen.

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Postoperative Pain Management: An Anesthesiologists' Opportunity And Challenge

To the Editor: We read with great interest the paper by Khalid A. Sami [1]. The description of all the various techniques of postoperative pain relief is very complete and will serve as a basis for lectures we give to our students at Sultan Qaboos University Hospital (SQUH) in Muscat, Sultanate of Oman.

Regarding intraspinal narcotics for regional analgesia, we do not agree with the statement "...patients who receive epidural narcotics should be admitted to ICU or step-down unit whenever possible" as we can foresee at least three problems: (1) very few ICUs would be able or willing to admit postoperative patients just for monitoring very rare respiratory depression due to intraspinal opioids; (2) admitting these patients to ICU increases the risk of nosocomial infections; and (3) family care, a major priority in the Middle East, is much less in ICU due to visitor restrictions.

It has been the routine at SQUH to provide postoperative pain relief with fentanyl and 0.125% bupivacaine in general surgical wards. This was initiated after a trial in our then, not busy, ICU and after proper training and information to the nursing staff in the wards. Patients receive, via an infusion pump, 3 to 8 mL of 0.125% bupivacaine solution containing 1 μg/mL of fentanyl. This is kept for a maximum of 48–hours; by this time, acceptable pain relief can be achieved with oral or parenteral analgesics. One anesthesiologist remains "on site" 24–hours a day to care for any related problems.

This technique is, to us, very safe. We do not expect any patient to develop respiratory depression with such a low dose of fentanyl. The only concern is to make certain that "spinal opioid" patients do not receive any additional opioids by any other route.

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Local Synthesis Of Immunoglobulins

To the Editor: The study by Daif AK [1] is very interesting and is proof of the development of neurosciences in Saudi Arabia.

The oligoclonal band is a good method supporting the evidence of intrathecal synthesis of immunoglobulins in infectious diseases in the central nervous system (CNS) [2].

Daif's paper is a very important contribution to the diagnosis of neurobrucellosis. Daif has applied the IgG index in a manner to demonstrate local production of immunoglobulins in cerebrospinal fluid (CSF) despite an increased CSF total protein level but, in 1987 a new, more integral formula more complicated to calculate, was published by Reiber and Felgenhauer [3].

Nevertheless, their formula has advantages which should be considered [3]. This formula is valid over both ranges of normal and pathological blood CSF barrier functions and has the ability to replace the IgG index reported, especially as it takes into consideration the loss of selectivity with increasing barrier impairment as an improvement on the earlier concepts of constant quotient ratios. In addition, among the formulas available for the calculation of intracerebral IgG, this one seems to be most appropriate, since it is not influenced by the collection volume such as the IgG index and can also be applied in all cases with blood-brain barrier disturbances [4].

The combination of oligoclonal bands and Reiber and Felgenhauers' formula should increase the diagnostic value in neurobrucellosis.

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Reply

To the Editor: We appreciate the comments of Dr. A.J. Dorta Contreras regarding a new formula to demonstrate local production of immunoglobulins in cerebrospinal fluid (CSF) which is valid over both ranges of the normal and pathological blood CSF barrier functions [1].

The most recent formula proposed by Reiber and Felgenhauer obtained the same percentage of positivity of the IgG index and was less influenced by the presence of a BBB damage compared with Tourtelotte, et al's [2] and Gallo et al's [3] formula. For routine purposes, the IgG index should be preferred because of its mathematical simplicity.

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Outpatient Neurological Practice In Saudi Arabia And Its Implications For Education In Neurology

To the Editor: Neurological disorders affect 2% to 6% of the population in industrialized countries [1], as presented in the literature and seen in Outpatient Clinics [1–4]. To our knowledge, little information is available about outpatient neurologic practices from Third World countries where health resources are limited.

In Saudi Arabia, the variables which influence neurologic practices in Western countries, mainly the demographic shift toward increasing geriatric medicine and the changing work habits of neurologists, are not applicable due to the younger age of the population [5]. Furthermore, the high incidence of consanguinity is likely to affect patterns of disease. During the past several years, the availability of modern noninvasive imaging technology has allowed much more precise diagnoses of neurological diseases.

This study was conducted in the Neurology Department at King Fahad Hospital of the University, Al-Khobar, which provides secondary and tertiary care to neurological patients in the eastern province of Saudi Arabia. All new cases including adults and children referred to the Neurology Clinic from July 1, 1984 to June 30, 1988 were included in the study. Patients' age, sex, and neurological diagnosis were documented. Investigations performed as required included brain computerized tomography, electroencephalography, electromyography, nerve conduction studies, cerebrospinal fluid studies, and appropriate biopsies, as well as blood and urine analysis.

Odd's Ratio (OR) was used to calculate the significance of the differences between our data and those published elsewhere (Table 1).

A total of 2,101 patients were examined during the study period. The mean age was 30 years

TABLE 1. *Comparison of the relative frequencies (%) of the neurological disorders in Saudi Arabia, United Kingdom (2–3), and United States (4).*

	Present study (n = 2101)	Hopkins et al (2) (n = 10236)	Perkin (3) (n = 7836)	Ringel et al (4) (n = 3000)	Odd's ratio
Epilepsy & convulsions	36%	12%	10.5%	10%	4.3
Headache	13%	13%	12.5%	19.5%	1.4
Peripheral neuropathy	13%	15%	9%	24%	1.29
Stroke	3.5%	6%	7.5%	5%	0.69
Muscle disorder/myasthenia gravis	3%	4%	–	2%	–
Parkinsonism	3%	4%	3%	4%	0.89
Amyotrophic lateral sclerosis	1%	2%	–	–	–
Syncope	1%	2%	2%	–	–
Multiple sclerosis	0.5%	6%	3.5%	5%	0.13
Dementia	0.5%	1%	1.5%	1.5%	0.6
Psychiatric disorders	2%	6%	7.5%	4%	0.27
Other or not diagnosed	13.5%	29%	43%	24%	–

The Odd's ratio as calculated between the actual number of patients (our study # sum of the 3 other studies). It was not calculated when some data were lacking.

(range: neonate–90 years). Thirty-five percent of the patients were children under 12-years-of-age. There were 1,128 (54%) males and 718 (46%) females. Saudi nationals constituted 78% of the cases. The most common disorders in all age groups were seizures (36%), headaches (13%), and peripheral neuropathies (13%). The latter included cranial nerve palsies (70), mononeuropathies such as carpal tunnel syndrome (50), root and plexus disorders, and the polyneuropathies.

The most common disorders in children were seizures (39%), mental retardation (22%), and cerebral palsy syndrome (15%). Twelve cases of spinal muscular atrophy type I (Werdning Hoffman disease) in addition to seven cases of subacute sclerosing panencephalitis were encountered in this age group.

Seizures constituted the most common disorder (38%) in adults and adolescents, 60-years or younger (1,219 cases), followed by headache syndromes (21%), and peripheral neuropathies (17%). Multiple sclerosis and myasthenia gravis were seen with the same frequency (0.5%). Basal ganglia disorders (2%) included Parkinson's disease, essential tremor, Sydenham chorea, dystonic disorders, and tics. Not a single case of Huntington's chorea was recorded. Cerebrovascular disorders (2.5%) were found to be relatively uncommon.

In elderly patients, aged 60-years or older (n = 157), the most common disorders were basal ganglia diseases mainly Parkinson's disease (23%), cerebrovascular diseases (23%), and peripheral neuropathies (13%). Only ten patients in this age group presented with dementia (7%).

In 114 patients (5%), an inherited neurological disorder was diagnosed (e.g., muscular dystrophies, spinal muscular atrophies, spinocerebellar degenerations, and neurocutaneous disorders, degenerative brain diseases). In another 225 (11%), a family history of a similar neurological disorders (e.g., epilepsy, cerebral palsy, and mental retardation) was given. These disorders were more frequent in Saudi patients while headache syndromes were found in equal frequencies in Saudis and expatriates. Neurobrucellosis was encountered in one case. Other infections were rare (11).

In the present study, headache, peripheral neuropathy, cerebrovascular disease, Parkinson's disease, and dementia had frequencies similar to those reported from Great Britain [2,3], and the USA [4] (OR = 0.6 to 1.4). However, a neurologist working in Saudi Arabia is more likely to see patients with seizures (OR = 4.3) than one working in Western countries. On the contrary, the chances of seeing multiple sclerosis are about seven times less (OR = 0.13) and those of psychiatric diseases four times less (OR = 0.27). These differences may simply be due to the referral system in Saudi Arabia where psychiatric patients are treated in specialized centers and epileptic patients are generally followed up in neurology clinics. The low frequency of multiple sclerosis in this study suggests a true reflection of its prevalance in the community since all such cases would have been seen by a neurologist.

Some differences in the pattern of neurological disease may be due to the relatively younger age group of the Saudi population and possible geographical and socioeconomical differences. Seizures, mental retardation, and cerebral palsy were common disorders in our practice probably because 35% of our patients were younger than 12-years-of-age.

Ringle et al [4] have proposed that, among other requirements for neurologic service, a demographic shift toward increasing geriatric medicine should be considered when planning for medical curricula or health manpower needs and the provision of facilities for management. Based on the findings in this study, recommendations can be made about undergraduate and postgraduate education in neurology in Saudi Arabia, and, by extension, the Arab world, in general. The content of our curricula tends presently to reflect conditions which are common in the prescribed textbooks rather than those which are actually prevalent in our communities. The training of medical students and postgraduates in Family Medicine should more usefully concentrate on these common disorders. These implications for postgraduate education are pertinent to not only trainee neurologists but also trainee internists and pediatricians.

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Endoscopic Insertion of Metal Stent For Malignant Biliary Stricture

To the Editor: Malignant obstructive jaundice is a very difficult management problem facing surgeons and gastroenterologists. In most cases only palliative measures can be offered to patients. The palliative management can be either surgical bypass or endoscopic internal drainage using different types of stents [1–5]. Small caliber stents are known to develop blockage resulting in cholangitis. Therefore, the recent development is toward large stents to prevent blocking. Unfortunately this is limited by the size of the endoscopic instrumental channel of the endoscope. Recent developments of self-expanding metal stents using a balloon to expand the stent and achieving large drainage channel of nearly 1 cm in diameter has been introduced in the last few years. The stent is made of stainless steel alloy filaments braided in a tubular way. For implantation the diameter is reduced by elongation. It is mounted on a catheter balloon which can be inflated to 5 atmosphere and after proper positioning this expands the stent to 7 mm to 9 mm in diameter. The balloon is then deflated leaving the stent in position and the catheter balloon is withdrawn.

We report the first two cases performed in our unit for inoperable malignant strictures using the metallic self-expanding stents.

Case 1

A 57-year-old male presented with complaints of abdominal pain, yellow discoloration of sclera and skin, and severe itching of a few weeks' duration accompanied by pale stools and dark urine. The patient was known to being diabetic and hypertensive.

On examination, the patient looked ill, pale, and was dehydrated. He had tachycardia and blood pressure was 100/80. The patient was deeply jaundiced. His liver and spleen were not palpable, there was no ascites. Investigation revealed hemoglobin 8.7 gm/L, WBC 6.1, platelets 21,000, prothrombin time 13.8 sec/L, SGOT 55 u/L, SGPT 140 u/L, alkaline phosphatase 202 u/L, SGOT 174 u/L, total bilirubin 212 μmol/L, direct bilirubin 173 μmol/L.

Computerized tomography (CT) of the liver showed obstruction of the left lobe and medial portion of the right lobe. There was a suspected tumor of the biliary tree.

Endoscopic retrograde cholangiopancreatiography (ERCP) revealed a blockage at the porta hepatis. A biopsy was taken and bile was sent for cytology.

The biopsy of the common hepatic duct was highly suspicious for carcinoma. The patient was considered to be unfit for surgery. Therefore an expandable endoprosthesis was introduced endoscopically (Figure 1a, 1b, 1c) and the patient was discharged home one week later in good condition.

Six months following insertion of the stent the patient was in fair general condition without recurrence of jaundice.

Case 2

An 85-year-old female was referred from another hospital with a diagnosis of malignant obstructive jaundice due to common hepatic duct malignancy. In the referring hospital she had an endoscopic retrograde cholangiopancreatiography (ERCP) with placement of a French size 8 endoprosthesis (2.7 mm diameter). Despite this and on admission to our unit, the patient had clinical evidence of obstructive jaundice and cholangitis. Emergency endoscopy revealed that the endoprosthesis was not functioning because of clotting. The endoprosthesis was replaced with a second French size 8 (2.7 mm diameter) endoprosthesis, which also became blocked seven days later. Percutaneous transhepatic cholangiography (PTC) showed blockage of the distal part of the common bile duct and percutaneous drainage was performed.

Because of the patient's poor general condition and as she was a high-risk surgical candidate with congestive heart failure, it was decided to place an

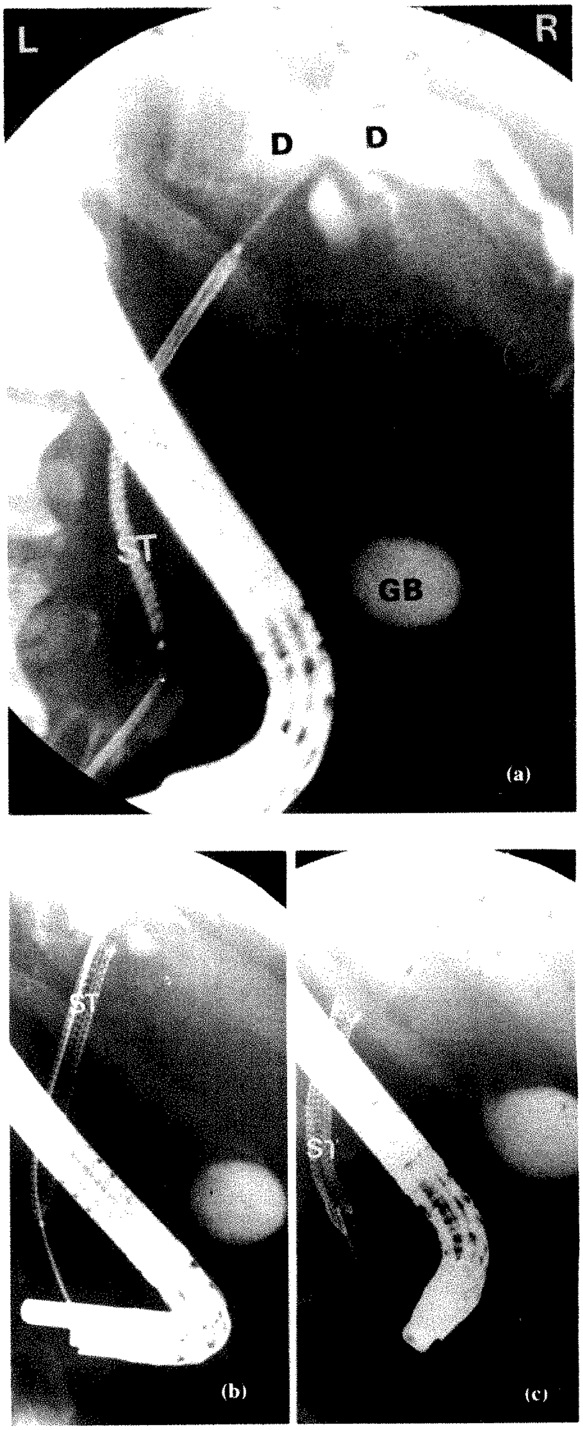

FIGURE 1. (a) Introduction of the deflated stent (ST) through the malignant stricture of common bile duct, cholangiogram also shows dilatation of the biliary tree proximal to the stricture (D) and gallbladder (GB); (b) after proper positioning, inflation of the balloon expanding the metal stent (ST); (c) balloon is withdrawn leaving stent (ST) in position with complete drainage of proximal biliary tree.

expandable endoprosthesis with a diameter after expansion of 8 mm (Figure 2a, 2b, 2c). The endoprosthesis is now functioning two months following insertion and the patient remains in relatively good condition.

Discussion

Early clotting of stents result in recurrence of jaundice. Cholangitis is frequently observed shortly after insertion of stents in the treatment of biliary stenosis [1–5]. Migration of the stents is also seen frequently [1–5]. Various attempts have been made in an attempt to prevent clotting of the endoprosthesis. It was evident that only the enlargement of the stent diameter seemed to prolong the time of the endo-prosthesis patency. However, this is limited by the diameter of the fiberoptic instrumentation channel [3]. The recent development of large lumen self-expanding endoprosthesis, which can be introduced either percutaneously or endoscopically, brings new hope of substantial improvement in the lumen size and prevention of clotting [3,4]. Neuhaus et al [5] reported on 19 stents inserted endoscopically and 34 stents inserted percutaneously on patients with malignant and benign biliary strictures. Huibregtse et al [6] reported also of another 33 patients with good results. Their impression was very positive with an excellent 30-day result and a better outcome on longer follow-up compared with ordinary stents. One disadvantage is that the prosthesis cannot be removed once it has been implanted.

Many centers in different countries all over the world have started using such prostheses for management of biliary stricture in the last few years.

With these two cases and the utilization of such expandable prostheses in our unit, we found that insertion is technically no more difficult than other types and has the advantage of improved therapeutic results with good drainage and no cholangitis on follow-up.

One important disadvantage of these endoprostheses are their high prices, as is usual in the early stages of marketing of such products. This is recouped by reduction of the need for reintervention. Moreover, we hope that the prices will be reduced with more usage of such a prosthesis. It is obvious that further studies for evaluation of these endoprostheses are awaited to clarify advantages and disadvantages of these stents.

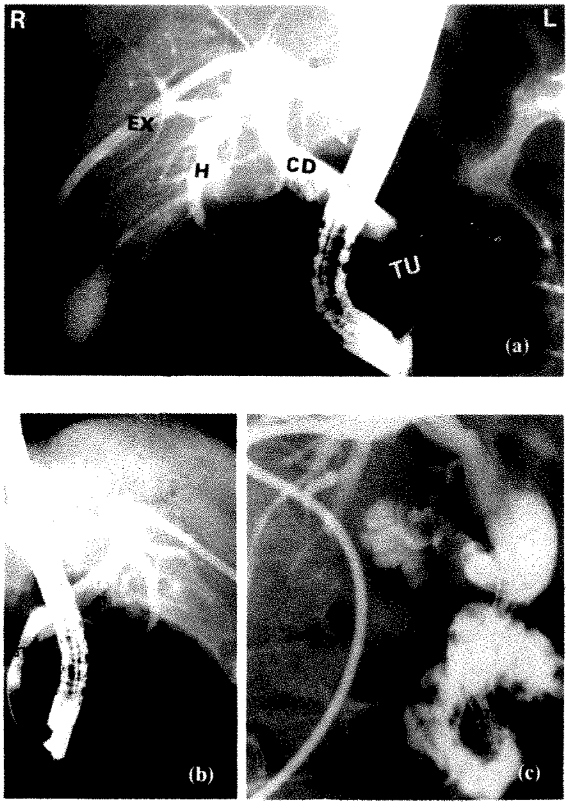

FIGURE 2. (a) ERCP showing stenosis (TU) in distal common bile duct with dilated proximal common bile duct (CD) and hepatic ducts (H) in situ; (b) after proper positioning, stent (ST) is expanded by balloon inflation; (c) stent (ST) in situ.

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An Unusual Presentation of Clear Cell Sarcoma

To the Editor: A 34-year-old left-handed British male was referred with a slightly painful "recurrent ganglion" over the dorsum of the right wrist of six months' duration. One month prior to presentation the patient noticed the appearance of another small lump over the dorsum of the right hand which was asymptomatic. The "ganglion" was curetted ten months prior to admission in an outside clinic under local anesthesia. There was no report of the original specimen being sent for pathology.

The patient underwent exploration and excision of both masses under regional block with a double tourniquet (Biers block). The dorsal wrist mass was found to originate from the sheath of the extensor carpi radialis brevis and adhering to the extensor retinaculum and dorsal capsule of the wrist. The dorsal wrist synovium was intact. The small mass over the dorsum of the right hand was originating from the sheath of the extensor tendon of the ring finger. Both were excised completely.

Pathologic Findings

The material presented consisted of: (1) an irregular piece of white rubbery tissue measuring 1.0 × 0.5 × 0.3 cm, all blocked; (2) a globular mass of pale gray rubbery tissue measuring 3.0 × 2.0 × 1.2 cm with a small segment of tendon tissue. On cut surface the mass was adherent to the tendon and was composed of pale gray soft tissue with areas of hemorrhage. Microscopically, the tumor was composed of nests and fascicles of polygonal rounded or spindle-shaped cells (Figure 1). They presented vesicular nuclei with very prominent single central nucleolei. The cytoplasm was abundant and often clear. Mitoses were frequent, climaxing to 4 per 10 high-power field, with an occasional atypical figure (Figure 2). In a few scattered fields there were multinucleated giant cells. Mucin and alcian blue stains were negative. Periodic acid-Schiff (PAS) stain gave a faintly positive response. Silver impregnation demonstrated a loose network of reticulin fibers that surrounded the tumor cells individually and in small nests. Fontana and iron stains did not react with tumor cells. Inconspicuous iron deposits were noted in the interstitium. The absence of demonstrable melanin in sections stained by the Fontana technique does not rule out the diagnosis of clear cell sarcoma (CCS) of the tendon sheath because melanin is demonstrable in only 50% of the cases [1,2].

This tumor is readily differentiated from synovial sarcoma because of the absence of biphasic cellular pattern and intracellular mucin formation. The presence of clear cells and the nesting of the tumor cells on silver impregnation speak against a fibrosarcoma. The differentiation of epithelioid malignant schwannoma or a spindle-cell melanoma is more difficult. The absence of

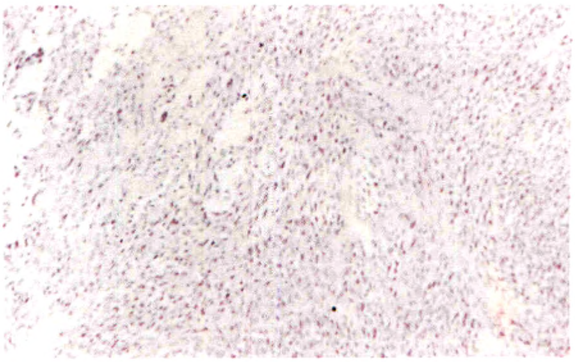

FIGURE 1. Cellular growth composed predominantly of spindle cells arranged in diversely oriented bands. Nests of polygonal cells presenting clear cytoplasm are also noted. (Original magnification, × 200.)

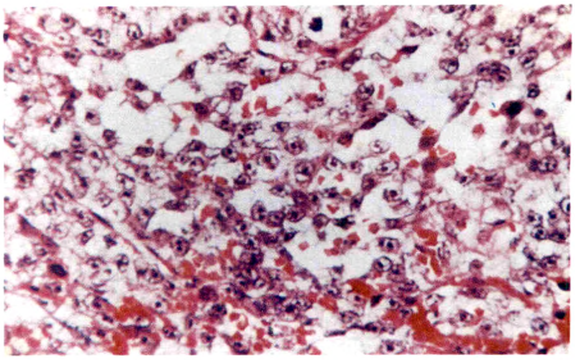

FIGURE 2. Higher power view. Predominance of polygonal cells with clear cytoplasm. Nuclei are vesicular with prominent nucleoli. A mitotic figure present near mid-upper border. (Original magnification, × 400.)

peripheral nerves within the vicinity and of any history of neurofibromatosis are arguments against the former. The total absence of skin involvement and the partial clear cell pattern speaks against spindle-cell melanoma [3].

Besides the identification by the protein S100 [1,3] other new techniques are now used to confirm the diagnosis of CCS such as ICR2 [5], a new monoclonal antibody to epithelial membrane antigen and HMB-45 [4] a melanin-associated antigen. On the other hand, cytogenetic techniques [2] are reported to demonstrate clonal, numerical and structural abnormalities with specific involvement of chromosome 2 and 22 in CCS.

Clear cell sarcoma or malignant melanoma of the soft tissues, is an uncommon tumor forming 2% of all the soft tissue sarcomas. For this tumor to present as a swelling in the dorsum of the wrist suggesting a recurrent ganglion is worth mentioning.

Clear cell sarcoma was originally described by Enzinger in 1968 [1]. Since then there have been reports on scattered cases and few reviews of the literature. These tumors are generally included in the neoplasms originating from the neural crest derivatives. Schwann cell origin was proposed but seemed unlikely for the reasons already mentioned. The presence of lymph node metastasis and intracellular glycogen speaks in favor of malignant melanoma. However, the presence of melanocytes in tendons and aponeurosis has never been recognized [5]. The positive reaction with PS 100 is additional proof in favor of malignant melanoma and clear cell sarcoma.

In spite of adequate therapy, prognosis in patients with clear cell sarcoma is not favorable. Most of the patients develop recurrences within 2.6 years and metastasis within 3.5 years. In one exceptional case, the patient remained alive 26-years after the diagnosis with four recurrences that were excised. The most common sites of metastasis are the regional lymph nodes, lungs, bones and to a lesser extent the myocardium [1].

Because of its highly malignant nature, the treatment of clear cell sarcoma includes radical excision (or amputation if radical excision is not possible), combined with radiotherapy and multiagent chemotherapy [5]. Regional lymph node excision should be part of the surgical procedure if the lymph nodes are clinically involved. Cure rate is not known since there are case reports of recurrences or metastasis ten or more years after extensive treatment. Our patient returned to his home country where a below-elbow amputation was performed followed by a course of radiation and chemotherapy.

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Extrapyramidal Reactions Caused By Metoclopramide In Children

To the Editor: Metoclopramide is an antiemetic drug which is available in drops, suppositories, tablets, and ampules. The mechanism of action is by antagonizing the effects of dopamine in the central nervous system (CNS) and other organ systems. Metoclopramide has been used for the treatment of gastroesophageal reflux, postsurgical gastroparesis, diabetic gastroparesis, gastric ulcer, and anorexia nervosa. Approved indications by the Federal Drug Administration (FDA), USA, includes facilitations for tube placement in the stomach and intestines, diabetic gastric stasis and short term use in gastroesophageal reflux and as an adjunct to anti-cancer chemotherapy [1]. The total daily dose in children should not exceed 0.5 mg/kg body weight and not more than 0.1 mg/kg per dose.

Side effects have been reported in up to 20% of patients [1]. These side effects are usually mild, transient, and reversible following withdrawal of the drug. Drowsiness and lassitude occurs in up to 10% of patients. Anxiety, restlessness, and motor agitation are dose-related and are more frequent following intravenous administration. Urticarial and maculopapular rash may be rarely seen. Extrapyramidal side effects are uncommon. True dystonia occurs in approximately 1% of patients. Other reactions include trismus, torticollis, facial spasms, opisthotonos and oculogyric crisis. These reactions disappear within 24-hours following discontinuation of the drug [21]. Symptoms of Parkinson's disease involving tremors, rigidity, and akinesia are rarely seen, except in cases where excessive doses have been administered or in patients with decreased renal function. Children are particularly susceptible in developing symptoms resembling parkinsonism [3]. These reactions respond rapidly to drugs such as diazepam or benztropine. In some adults, long-term administration may lead to breast enlargement or nipple tenderness, galactorrhea, and menstrual disorders [1]. Metoclopramide is most likely to cross the placenta; its safety for the growing fetus and nursing infant has not been established [4].

A retrospective analysis was made of records of patients admitted to Sulemania Children's Hospital from September 1985 to July 1990 with extrapyramidal reactions following administration of metoclopramide. In this analysis, 25 patients were identified. The records were analyzed for age, sex, dose of the drug, interval of administration, clinical features, laboratory investigations, and therapeutic interventions. Eight patients were male, 15 patients were younger than six months of age, 21 younger than 12 months, and four patients being one-year-old. The youngest patient was 2½ months and the oldest 10½ years. Twenty patients were Saudi. Metoclopramide was administered therapeutically to all of our patients to control vomiting. The dose could not be calculated for the majority of patients. The interval period between administration of the drug and appearance of symptoms varied between 20 to 36 hours. The diagnoses for which metoclopramide was prescribed included gastroenteritis (15), upper respiratory tract infection (5), and others (5). These patients presented with various types of extrapyramidal reactions such as oculogyric crisis, opisthotonos, convulsions, hypertonia and conjugate deviation of eyes and nystagmus. The most frequently presenting manifestation was oculogyric crisis. Generalized convulsions are rarely seen as a manifestation of metoclopramide idiosyncratic reaction. The patients in our study may have been labeled as having convulsions by the Emergency Department physician on admission, while the patient may have actually been presenting dystonic reaction. On admission, all patients were alert except one who was drowsy. Table 1 demonstrates various types of extrapyramidal reactions observed at the time of admission. The symptoms disappeared within 24 hours following discontinuation of the drug. Lumbar puncture was performed on five patients with a suspicion of meningitis, one of whom was drowsy on admission. Cerebrospinal fluid was normal in all the patients.

The current role of antiemetics in the management of nausea and vomiting in children is, at best, considered to be controversial. With the widespread use of oral rehydration solutions in the management of gastroenteritis, there seems to be a gradual disappearance of drugs used for controlling vomiting. Low and Goel [5] reported 15 children with metoclopramide poisoning. In their study, all ten patients with extrapyramidal reactions were being treated with a dose of > 0.5 mg/kg of metoclopramide a day. There are other reports of extrapyramidal side effects observed in children who were overdosed with metaclopramide [6]. However, alarming dystonic reac-

TABLE 1. *Symptoms and signs in 25 patients.*

Symptoms and signs	Number of patients*
Oculogyric crisis	14
Opisthotonos	10
Convulsions	7
Increased muscle tone in limbs	6
Conjugate deviation of eyes	1
Nystagmus	1

* Total number of patients 25, some of symptoms and signs were exhibited by the same patients.

tions have been reported even with recommended doses [3]. Because of the retrospective nature of this study, we were unable to determine the exact dosages of drugs received by our patients. Eighty percent of our patients received the drug for vomiting associated with either gastroenteritis or upper respiratory infections. The most frequently presenting manifestation was oculogyric crisis followed by opisthotonos and convulsions. Most patients developed symptoms 20 to 36 hours following the initiation of metoclopramide. All symptoms resolved within 24-hours following discontinuation of the drug.

Dystonic reactions are distressing for parents. There may also be unnecessary hospital admissions as well as uncomfortable procedures for patients such as lumbar puncture. We recommend avoiding the use of metoclopramide for vomiting associated with gastroenteritis.

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Increased Chromosomal Aberration and Expression of Specific Breakpoints After Chronic Irradiation of Fibroblasts From A Patient with Non-Hodgkin's Lymphoma

To the Editor: Despite the proposed association between DNA repair defects and increased susceptibility to cancer in inherited disorders like ataxia telangiectasia (AT) and xeroderma pigmentosum (XP), the mechanisms underlying this important link have remained poorly understood [1]. Normal body cells from these syndromes, particularly AT and even AT-heterozygotes have been found to exhibit enhanced sensitivity to radiation *in vitro* [2]. It is believed that the asymptomatic AT-heterozygotes carry at least a 2–3 fold higher risk of dying from a malignant disease and that this potentially "high risk" group alone comprises more than 2–3% of the so-called normal population [3]. These findings stimulated a great deal of interest in exploring the usefulness of *in vitro* cellular radiosensitivity for the identification of cancer-prone individuals. While cell lines from several cancer-prone disorders other than AT and XP and also some cancer patients have been isolated and their *in vitro* cellular radiosensitivity demonstrated [4,5] little effort has been made in showing the genetic connection between carcinogen-sensitivity and cancer risks by analyzing chromosomal and mutational alterations in these cells.

We have recently reported that skin fibroblast cell lines from most of the Saudi patients with non-Hodgkin's lymphoma (NHL) showed increased sensitivity to chronic gamma irradiation [5]. In the present study, we examined one of these radiosensitive cell lines (L 213725) for chromosomal aberration and specific breakpoints after chronic irradiation compared to the cell lines from a normal subject and an AT patient.

Skin fibroblast cell lines developed from cutaneous biopsies obtained from NHL and AT patients as well as normal subjects have been described [5]. Early passage (4–10) cells were grown in Ham's F12 medium supplemented with glutamin (2mM), penicillin (100 μg/ml) and 10–15% fetal bovine serum in 100 mm tissue culture plates, and incubated at 37°C in a humidified (80%) atmosphere with 5% CO_2, 95% air. Cells from the exponential growth phase were harvested, replated in F12 medium and grown to confluence. The plates with confluent cell cultures were irradiated in CO_2 incubator, using a ^{60}Co medical Gamma source (International Neutronics, Inc., Palo Alto, California, USA), at a dose rate of 0.008 Gy/min. Following irradiation, the growth medium was renewed and the plates were left in a CO_2 incubator overnight. For survival analysis, cells exposed to different doses of radiation were then trypsinized and seeded at a density of 200–20,000 per plate (depending upon radiation dose) together with a feeder layer consisting of radiation (50 Gy) inactivated human fibroblasts (60,000/plate). After further incubation with a weekly change of medium for up to three weeks, the plates were washed with phosphate-buffered saline and stained with crystal violet to count the macroscopic colonies (> 50 cells/colony) as survivors. The percent survival for each cell line was calculated based on the respective unirradiated survivors serving as controls and the survival curves were plotted on semi log paper to illustrate the difference in cellular radiosensitivity of the cell lines studied.

For cytogenic studies, irradiated cells that were incubated overnight were trypsinized, replated and grown for 48-hours. Colcemid was added to the cells at a concentration of 0.05 mg/ml for one hour before harvesting them by trypsinization. Cells were then exposed to a 0.075 M hypotonic KCl solution at 37°C for 20 min. and fixed in cold 1:3 acetic acid/methanol for one hour. The suspended cells were dropped on pre-cleaned, chilled slides and the chromosomes were trypsin-Giemsa banded. Chromosome analysis in each cell line was performed on 100 (coded) banded metaphases at each radiation dose-point. Breaks and rearrangements (i.e., rings, translocations, inversions, dicentrics) were scored as chromosome aberrations, and the Karyotypic analysis was performed as defined by ISCN (1985) nomenclature.

An increased sensitivity of fibroblast cell lines from NHL patients to chronic gamma-irradiation has been already reported [5]. Figure 1 illustrates the survival curves obtained after chronic irradiation of cultured fibroblasts from one NHL patient, one AT patient and a normal subject used in the present study. Experiments with these cell lines were repeated three to five times and their D_{10} (radiation doses resulting in 10% survival) values (in cGy) estimated from the survival curves, were 840–900 for the normal subject, 213–390 for the NHL patient and 150–280 for the AT patient. The cell line from the NHL patient clearly occupied an intermediate position between the normal subject and the known radiosensitive syndrome AT. These data are consistent with the radiation response of NHL patients' cells we observed earlier [5]. The data presented in Table 1 show the frequencies of chromosomal aberration in the 3 cell lines after irradiation at two different doses. These results, like the cell survival data, demonstrate an intermediate chromosomal radiosensitivity of the cell line derived from the lymphoma patient.

A careful examination of the karyotypes in the cell line originating from the NHL patient showed at least 2% cells with chromosomal breaks in the regions 2p12–13 and 8q22–24 resulting from 1.8 Gy chronic gamma-irradiation (Figure 2). These breakpoints correspond to the fragile sites described by other investigators and are involved in the characteristic translocations such as t(8;14) (q24;q32), t(8;22) (q24;q11), t(2;8) (p12;24), often found in lymphoma and leukemia [6,7]. Furthermore, two important oncogenes, the N-myc and c-myc, have been assigned to the region 2p23–24, and 8q24, respectively, indicating the potential oncogenic significance of chromosomal breakage at or near these regions [6,7]. A study of similar number of metaphase chromosomes from the normal subject did not show any specific breakpoints as in the NHL patient, and the AT cell line had too many breaks making the assessment difficult.

Our observations that the fibroblast cells from an NHL patient show both cellular and

TABLE 1. *Frequencies of radiation induced chromosome aberrations in fibroblast cells from a normal subject, an NHL and an AT patient.*

		Chromosome aberrations/100 cells			
Source of Cell line	Radiation dose in Gy	Breaks	Trans-location/ inversion	Rings/ Dicent-trics	Average breaks/ cell
Normal subject	0	5	–	–	0.05
	1.8	8	1	–	0.10
	4.6	18	3	–	0.24
NHL patient	0	7	3	–	0.13
	1.8	30	12	2	0.58
	4.6	48	48	6	1.56
AT patient	0	20	9	1	0.40
	1.8	44	34	4	1.20
	4.6	176	172	15	5.50

NHL = Non-Hodgkin's lymphoma; AT = ataxia telangiectasia

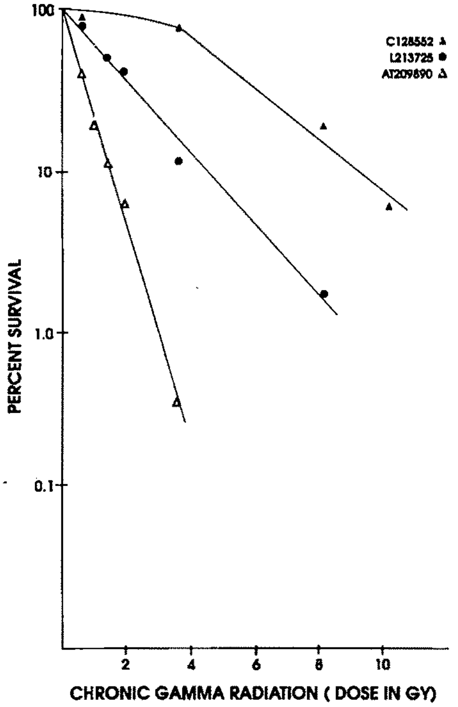

FIGURE 1. Survival curves of three fibroblast cell lines after chronic gamma-irradiation: C128552 (normal subject), L13725 (NHL patient) and At209890 (AT patient).

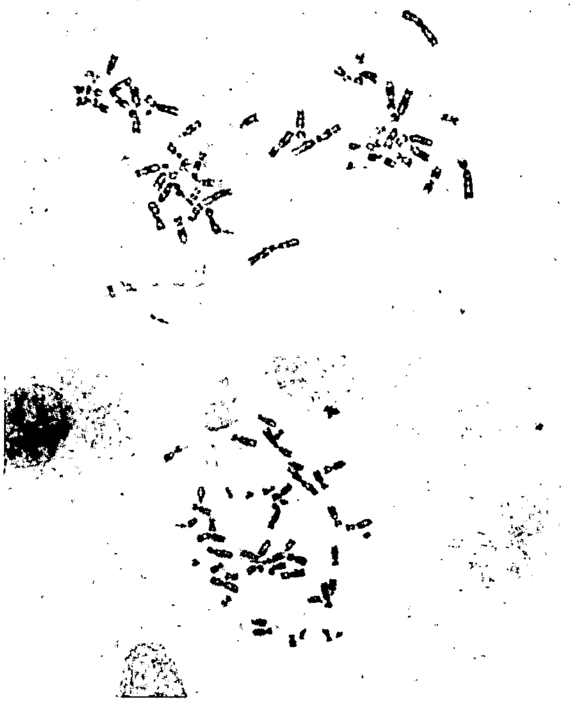

FIGURE 2. Chromosomes in the fibroblast cells from the NHL patient showing radiation-induced specific breakpoints. Arrows indicating specific breakpoints in (A) chromosome 8 ie 8q22-q24 and (B) chromosome 2 ie 2 p 12-13.

chromosomal radiosensitivity suggest the existence of a defective repair process concerned with rejoining of radiation induced DNA strand breaks in this and perhaps other patients. However, the detection of fragile sites expressed after chronic irradiation of the cells of the patient examined in this study indicated that chromosomal breakpoint "hotspots" may result from exposure to certain carcinogens in these patients because of a defect in a specific repair process. Further studies using more cell lines are needed to find whether or not chronic radiation-induced fragile sites are associated with most of the NHL patients. Meanwhile, the observation of cellular and chromosomal radiosensitivity resulting in the occurrence of specific breakpoints at or near the known oncogenes in the fibroblasts from the NHL patient we studied may explain the genetic basis of the connection between increased radiosensitivity and the risk of oncogenic development. One would presume that the patient was already predisposed to malignancy. Studies aimed at detecting similar chromosomal fragile sites in fibroblasts and actual tumor cells in the same patients will provide further clues to genetic basis of cancer susceptibility, and oncogenic development.

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Symposium Abstracts

THIRD INTERNATIONAL SYMPOSIUM ON MULTIDISCIPLINARY MANAGEMENT IN SOFT TISSUE AND BONE SARCOMAS

Sponsored by and conducted at King Faisal Specialist
Hospital and Research Centre, Riyadh
11–12 February 1992

RHABDOMYOSARCOMAS OF THE ORBIT: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE EXPERIENCE, M Abuzeid, K Taibah, Z Mahasin, K Sackey, S El-Akkad, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980–1991 a total of 100 cases of rhabdomyosarcoma (RMS) were seen at King Faisal Specialist Hospital and Research Centre (KFSH&RC). Forty-five of these cases were in the head and neck region (45%). Thirty-one (31%) were children younger than five years of age. Eighteen cases (58%) presented in the head and neck region, and 16 (89%) were orbital RMS. Out of 16 cases, 13 were alive for more than three years (81%). This is comparable with the 83% survival rate recorded in the literature, in spite of the late referral of cases with advanced disease (75% group 3), poor follow-up and emigration of some patients out of Saudi Arabia. All cases were treated with adjuvant chemotherapy and most of them with radiation therapy. Surgery was in the form of biopsy only except for 2 cases who had radical surgery for residual disease after chemotherapy and radiation therapy. Although surgery has had a small role in the treatment of orbital RMS in the last 24 years, it might be adopted more and more as advances and experience in skull base surgery, reconstructive and microvascular surgical skills continue to accumulate.

SOFT TISSUE SARCOMA: KUWAIT EXPERIENCE, JA Ahmed, YT Omar, SM Ali, L Temmim, Kuwait Cancer Control Centre, Kuwait

A retrospective study of patients with diagnosis of soft tissue sarcomas seen in the Kuwait Cancer Control Centre was carried out during the period of 1974–1987. The results were analyzed with respect to clinical characteristics, some of the prognostic factors and survival rates. One hundred seventy-two cases were analyzed, 128 were males and 44 females with a male to female ratio of 3:1. The median age was 38 years. Sixty-three percent had liposarcoma, fibrosarcoma, rhabdomyosarcoma and malignant fibrous histiocytoma. The most common region involved was the lower extremity followed by the trunk. The treatment in most cases was surgery and adjuvant radiotherapy. Five year actuarial survival rate was 30% which was calculated for only 114 patients analyzed until December 1982. The overall rate of local recurrence was 33%. Local failure was highest in abdominal tumors (72%). In extremity lesions, local recurrence was higher in proximal sites than in distal sites. Twenty-eight percent of the patients had metastases, the lung being the most common organ (68%). The histological type had no bearing on local failure or dissemination. The rate of local recurrence and metastases was higher in high grade than low grade tumors. In conclusion, the histopathological grade was found to be the most important prognostic indicator both for local recurrence and metastases.

NEUTRON THERAPY SOFT TISSUE SARCOMAS: A REVIEW, S El-Akkad, H Schultz, M El-Senoussi, R Wierzbicki, I Christophersen, H Abdallah, S Devi, King Faisal Specialist Hospital and Research Centre, Riyadh

The Neutron Therapy Program at the King Faisal Specialist Hospital and Research Centre (KFSH&RC) was initiated in April 1987 using our cyclotron CS 30 to produce a (p(26)+Be) reaction. Our first study conducted focused on head and neck cancers which established an optimum neutron dose of 1860 cGy in 12 treatments over four weeks. This was based upon our radiobiological data and validated by our previous dose searching study. Another study aimed at testing the benefit of neutrons in soft tissue sarcomas has recently been initiated. At King Faisal Specialist Hospital and Research Centre (KFSH&RC) approximately 60 patients are referred annually with the diagnosis of soft tissue sarcomas which constitutes 3% of the total annual cancer referrals. A retrospective analysis has shown that 25% of these cases were localized soft tissue sarcomas of the extremities or extra-thoracic/extra-abdominal trunk with a prevalence of lower extremity sarcomas. An additional 12% had distant metastases at presentation. The remainder were either postoperative cases with no gross disease or patients who were beyond any treatment. World literature has shown that neutrons improve the local control of soft tissue sarcomas as compared to photons. Local control rates in the range of 36–93% were reported, depending on the grade and stage of disease, its operability, and the type and extent of surgery performed. A study of 27 cases treated by neutrons with no gross residual disease following radical surgery showed 93% local control and 74% survival. Another study with data compiled from a series of patients treated in 16 centers using either photons or neutrons for the treatment of de novo or postoperative gross disease revealed a local control rate of 53% in 297 patients treated by neutrons as compared to 38% in 128 patients treated by photons. Encouraged by these results, our patients with locally advanced inoperable tumors or with postoperative gross disease as well as patients with distant metastases will be treated with this modality.

MALIGNANT BONE TUMORS IN PREGNANCY, M Sadat-Ali, E Ibrahim, College of Medicine and Medical Sciences, King Faisal University, Dammam

Two cases of malignant bone tumors in pregnancy are presented, one Ewing's and the other osteogenic sarcoma. The diagnosis of osteosarcoma was made during the first trimester and the patient did not accept any treatment until delivery. The patient underwent local resection of the tumor and chemotherapy after delivery of a healthy baby boy. The patient with Ewing's sarcoma presented during her last trimester; amputation and chemotherapy were instituted after induction of delivery. Our patients delivered healthy babies without any signs of maternal malignant disease. Pregnancy did not appear to accelerate the tumor growth nor in any way did it affect the ultimate outcome of the patients. The optimum management is not clearly defined due to the rarity of the condition and limited individual experience. A literature review with regard to available options of management will be discussed.

EFFECTS OF CHEMOTHERAPY ON VIABILITY OF TUMOR CELLS IN OSTEOSARCOMA, J Antonius, M Akhtar, MA Ali, A Ali, B Hainau, King Faisal Specialist Hospital and Research Centre, Riyadh

Surgically resected specimens from 12 patients with peripheral osteogenic sarcomas treated with adjuvant chemotherapy were studied histologically by complete blocking of a full midline section of the bone. Areas of viability and necrosis were mapped on graph paper and a quantitative assessment of dead and viable tumor tissue was made. In one case no viable tumor was found. In another case, viable tumor was found involving the articular cartilage, medullary bone in nine cases, cortex in nine, subcortical in eight cases, periosteum in nine, soft tissues in six cases, and joint ligaments in two. Tumor cells showing preserved cellular detail but with hyperchromatic and smudged nuclei, and cells with fine cleared nuclear chromatin and defined nuclear membranes were graded as viable. Areas without morphologically identifiable cells, and cells that were ghost outlines only were coded as necrosis. One case showed 100% unequivocal necrosis of all tumor. One case had .3% viable tumor. There was 80–99% tumor necrosis in four cases, 50–80% tumor necrosis in two cases, and there was 50% or less tumor necrosis in four cases. In conclusion, neoadjuvant therapy is an effective treatment for osteogenic sarcoma, in two out of three cases killing more than 50% of the tumor cells and in two cases killing more than .99% of the tumor. Mapping of surviving tumor is tedious but practical. There is still no absolute method in predicting the viability of surviving cells. This is estimated on the basis of histological appearance which may not be entirely accurate in predicting when tumor cells are dead.

STAGING OF MUSCULOSKELETAL SARCOMAS AND TECHNIQUES OF BIOPSY, R Asirvatham, King Faisal Specialist Hospital and Research Centre, Riyadh

A staging system and a common terminology to define surgical procedures are essential in making a meaningful comparison of different surgical procedures. In 1980 a system for the surgical staging of musculoskeletal sarcoma was devised by Enneking et al. Stage IA lowgrade intracompartmental, IB lowgrade extracompartmental, IIA highgrade intracompartmental, IIB highgrade extracompartmental and III presence of metastases, irrespective of histologic grade and tumor extent. Four types of surgical margins obtainable by four types of surgical procedures have been described. An intralesional margin is obtained as in debulking or curettage. A borderline margin is obtained by excising the tumor in one piece where the dissection runs through the reactive zone. A wide margin is accomplished by excising the tumor along with a cuff of surrounding normal tissue. In radical resection, the entire compartment(s) involved by the tumor is resected. Biopsy should preferably be performed by the surgeon who will be doing the definitive procedure. A correctly-placed biopsy tract should be capable of being excised en bloc along with the tumor during a subsequent definitive procedure. Transverse incisions are almost always contraindicated as they cannot be excised en bloc with longitudinally directed segments of bone. Contamination of major neurovascular structures should be avoided. Meticulous hemostasis is necessary since a hematoma opens tissue planes causing wide contamination. Drains are not recommended. A subcuticular closure permits a narrower ellipse of skin to be removed.

KOTZ MODULAR ENDOPROSTHESIS FOR RECONSTRUCTION FOLLOWING TUMOR RESECTION: A PRELIMINARY REPORT, R Asirvatham, PG Moreau, SM Kadhi, R Wierzbicki, AA El-Warith, King Faisal Specialist Hospital and Research Centre, Riyadh

Resection of advanced bone neoplasms often results in a large skeletal defect. Currently accepted methods of reconstruction of such defects such as allografts and custom-made endoprostheses are not available in the Kingdom of Saudi Arabia. We have been using the Kotz modular femur-knee-tibia reconstruction system since October 1990. The purpose of this paper is to report preliminary results. Between October 1990 and October 1991, reconstruction of skeletal defects with Kotz modular endoprosthesis was performed in seven patients at the King Faisal Specialist Hospital and Research Centre (KFSH&RC). There were five males and two females, aged 17, 23, 25, 35, 58 and 70 years, respectively. Four patients had tumor involving the distal femur (osteosarcoma 2, fibrosarcoma of bone 1, and giant-cell tumor 1) and one patient had a recurrent giant-cell tumor of the proximal femur. The remaining two patients had a revised hip arthroplasty utilizing Kotz femoral replacement endoprosthesis. Neoadjuvant chemotherapy with adriamycin and cisplatinum was given to both patients with osteosarcoma and the single patient with fibrosarcoma. There were two surgical complications. In one patient, the axle of the knee joint slipped requiring reinsertion. In another patient, the hip dislocated postoperatively. The margins of resection were free of tumor in all patients. Although our follow-up is short, we found the early results of Kotz endoprosthetic reconstruction in a small group of patients encouraging.

ROLE OF SURGERY FOR THE TREATMENT OF EWING'S SARCOMA OF BONE, R Asirvatham, PG Moreau, SM Kadhi, R Wierzbicki, AA El-Warith, K Sackey, King Faisal Specialist Hospital and Research Centre, Riyadh

Ewing's sarcoma (ES) has been traditionally treated with combination chemotherapy (CT) for systemic control and radiation (RT) for local control. Recently there has been a trend towards surgical resection over RT to avoid late complications of RT and possibly improve local control. Between 1982 and 1990, 18 patients with a median age of 14.5 years (M:F = 12.6) underwent surgery for local control of ES at King Faisal Specialist Hospital and Research Centre (KFSH&RC). In Group A, comprising ten resections, surgery was opted for local control after induction with CAV or VIP. (Time from diagnosis to surgery median 4.3 months; range one week-ten months). In three out of ten patients, postoperative RT was given (resection margin not free in one patient, one patient refused postoperative CT, and unknown reason one patient). After a median follow-up of 19.5 months since diagnosis (range 11–98 months), seven of ten patients were alive. Three of ten patients died (local recurrence (LR) and distant metastases (DM) in two patients and LR only in one patient). In Group B, eight patients underwent surgery (two resections and 67 amputations) after failure of CT and RT to control the tumor locally (time from diagnosis to surgery median 15 months; range 5–69 months). After a median follow-up of 25.5 months since diagnosis (range 10–78 months), there was one LR. Seven out of eight patients died of DM, 92 patients had DM preoperatively, and five developed DM postoperatively. Although the number of patients in this retrospective study was small, the following conclusions may be drawn. Surgery appears to be effective in obtaining local control of ES, both when chosen primarily and when RT has failed to obtain local control. When surgery is considered, it must be performed early, (not after RT), since longer intervals from diagnosis to surgery, increases the propensity toward metastatic disease.

ROLE OF MAGNETIC RESONANCE IMAGING (MRI) IN DETECTING RESIDUAL SOFT TISSUE SARCOMA,

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Surgeons are occasionally surprised when the histopathology following excision of a "lump" is reported as a soft tissue sarcoma (STS). It is a dilemma for an orthopedic oncologist to decide whether there is a residual STS, and if so, its extent. Between June 1990 and October 1991, 30 patients with STS were evaluated at the Combined Sarcoma Clinic at the King Faisal Specialist Hospital and Research Centre (KFSH&RC). There was no clinical evidence of a residual mass in eight patients who were referred after "excision" of an unsuspected STS. Bone scan, computerized tomography with intravenous contrast and MRI were performed in all eight patients. In addition to T1 and T2 weighted images (MRI), STIR technique was employed in some cases to reduce the signal from fat, and to amplify the contrast between the abnormal tissue and the surrounding normal soft tissues. Resection of possible residual tumor was performed in all patients and histopathology correlated with MRI findings. In conclusion, MRI was very sensitive to postoperative changes such as edema and hematoma and to any residual tumor. It was also very helpful to delineate the extent of the postoperative changes and/or residual tumor. However, based on MRI findings it was not possible to differentiate between the postoperative changes and residual tumor.

CHONDROSARCOMA: A CLINICOPATHOLOGICAL ANALYSIS,

R Asirvatham, RJ Rooney, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Chondrosarcomas (CS) are rare neoplasms representing only 10% of all malignant bone tumors. Between October 1978 and March 1989, 47 cases (M:F = 25.22) of CS with a median age of 46 years (range 8–71 years) were seen at King Faisal Specialist Hospital and Research Centre (KFSH&RC). Four had secondary CS. Fourteen out of forty-seven patients had variants of CS, i.e., clear-cell CS, one de-differentiated, eight myxoid, and four mesenchymal CS. Twenty-two out of forty-seven patients with CS were histologically Grade I, 22/47 Grade II, and 3/47 Grade III. Surgical staging, as recommended by the Musculoskeletal Tumor Society, revealed 14 patients in Stage IB, 24 in Stage IIB, and nine patients in Stage III. Seven out of forty-seven patients had CS located in the femur, and 9/47 in other locations including two extraskeletal. Of 47 patients, five were seen as consults only, 11 were inoperable, and two refused amputation. The remaining 29/47 patients were surgically treated at King Faisal Specialist Hospital and Research Centre (KFSH&RC)–4 amputations and 25 resections. The margins obtained were radical in two patients, wide in 13 (2/13 contaminated), marginal eight (1/8 contaminated), and intralesional six. After a mean follow-up of 2.7 years (range 0.5–6 years), 1/29 patients developed a local recurrence. Of 29 patients, four developed distant metastases. Of 29 patients, 21 are alive, except one patient with disease. In this retrospective review, the demographic details of CS in a Saudi population is presented. A high incidence of inoperability and poor survival is thought to be due to late presentation with advanced tumors.

RECONSTRUCTION OF SKELETAL DEFECTS AFTER TUMOR RESECTION: AN INNOVATIVE TECHNIQUE,

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In Saudi Arabia, reconstruction of skeletal defects after tumor resection is challenging because of large defects resulting from resection of advanced tumors and the unavailability of allografts and custom-made prostheses. Between 1987 and 1989, 24 patients underwent 27 reconstructions of skeletal defects (including three revisions) resulting from resection of bone neoplasms. There were 9 males and 15 females with a mean age of 23.6 years. Resections were performed for osteosarcomas in more than half of the patients. In 12 patients, the defect resulted from the knee fused with two stacked Kuntscher rods reinforced with PMMA cement. Intercalary defects were reconstructed using two long blade plates bolted end-to-end and reinforced with a Kuntscher nail and PMMA. The rods failed in two patients who as a result, required revision surgery. This technique is inexpensive, simple, and uses material commonly available in most hospitals worldwide. It provides a stable leg which allows immediate full weight bearing and is particularly advantageous for those who have a poor life expectancy because of late presentation or those patients who refused chemotherapy. Skeletal defects found in other locations were reconstructed with improvisation of available material, utilizing PMMA cement reinforced with endoprosthesis or intramedullary rods. The short-term results after reconstruction have been satisfactory.

MALIGNANT FIBROUS HISTIOCYTOMA OF SOFT TISSUES: A CLINICOPATHOLOGICAL REVIEW,

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The following retrospective study includes 52 cases of malignant fibrous histiocytoma of soft tissues presented to the National Cancer Institute of Cairo (NCI) from 1978 to 1987. This disease occurs mainly in adults older than 40 years of age. The male to female ratio was 2.4:1. The extremities were the most common site affected accounting for 62% of cases, followed by the trunk 31%, and the head and neck 7%. The most common pathological subtype was the spindle-storiform (36%), followed by inflammatory (30%), myxoid (25%), and giant cell subtype (3%). Subtyping was not possible in 5% of the cases. The five-year actuarial survival rate accounted to 40+ 12%, local recurrence occurred in 48% of cases, and distant metastases in 52% of the cases. The most important prognostic factors were the size of the tumor, its depth of infiltration, degree of differentiation, and site. Patients whose tumors were completely excised were accompanied by a better disease-free survival than those whose tumors were not completely excised (50% versus 16%, respectively). The addition of postoperative radiotherapy did not improve either the local control nor the survival of patients. This was attributed to the fact that most of the tumors which received postoperative radiotherapy were T(3) or T(4) and of a high grade, while those treated along with surgery were early, T(1) and T(2) tumors, mostly of low grade. Finally, adjuvant chemotherapy was given to three patients only and did not affect the local control of the survival of these patients.

VULVAR SARCOMA: REPORT OF FOUR CASES, YN Bakri, M Akhtar, M El-Senoussi, R Wierzbicki, King Faisal Specialist Hospital and Research Centre, Riyadh

Charts of 640 patients with soft tissue sarcomas presenting at King Faisal Specialist Hospital and Research Centre (KFSH&RC) from 1978 to 1991 were reviewed. Four patients with primary sarcoma of the vulva were identified. Since less than 30 cases were reported in the literature, this abstract will present characteristics of patients as follows: median age 20 (range 17–41); histology: leiomyosarcoma 3/4 patients, rhabdomyosarcoma 1/4 patients, association with pregnancy 2/4 patients. All patients had multiple local recurrence treated with surgery and/or plus radiotherapy. Two patients presented with localized disease and subsequently developed metastasis, and one patient presented with pulmonary metastasis, and one patient presented with extensive locoregional lymphadenopathy. Palliative chemotherapy with adriamycin-based regimens was ineffective in three patients while adjunctive chemotherapy for patients with rhabdomyosarcoma-induced PR. Median survival time for three patients (fourth patient with rhabdomyosarcoma just completed treatment) is nine years from original presentation. The original grade at initial surgery is unknown for most patients, but was assumed to be low grade. At the time of metastasis it was determined to be Grade 3 with the exception of one patient who had Grade 1 with focal epithelial changes.

ADJUVANT CHEMOTHERAPY FOR SOFT TISSUE SARCOMA, VHC Bramwell, London Regional Cancer Centre, Ontario, Canada

Even with good local control, metastases occurs in 30–50% of cases with soft tissue sarcoma. The role of adjuvant chemotherapy in preventing manifestation of metastases (and possibly improving local control) is a controversial issue. There have been a number of randomized trials in which patients receiving a variety of chemotherapy regimens have been compared with a concurrent control group not receiving chemotherapy. All have had significant flaws, but two (inadequate accrual and ineffective chemotherapy) are of major significance and affect most studies. Thus, although two small trials suggest that adjuvant treatment with doxorubicin or combination chemotherapy prolongs relapse free and overall survival, the results of seven other trials demonstrate only improvements in local control or no significant benefit. There are many theoretical reasons to support commencing adjuvant chemotherapy as soon as possible after diagnosis and, in reported studies, this time interval was highly variable. It is perhaps significant that chemotherapy was commenced early in the two studies showing the most benefit, although this was also true for the Boston study in which results were negative. In the EORTC trial, a median of six weeks elapsed between surgery and commencement of chemotherapy. A new EORTFC study in which a group of patients receiving preoperative doxorubicin plus ifosfamide (IFOS) is compared with a control group, addresses this issue.

A STUDY ON SOFT TISSUE SARCOMA OF THE FEMALE GENITAL TRACT, I Christophersen, S El-Akkad, H Schultz, M El-Senoussi, H Abdallah, SM Kadhi, R Wierzbicki, K Sackey, Y Bakri, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and 1991, a total of 23 patients with soft tissue sarcoma (STS) of the female genital tract were seen at the King Faisal Specialist Hospital and Research Centre (KFSH&RC). These were grouped as follows: Group A: Five children with embryonal rhabdomyosarcoma in the vagina; median age 3.7 years (range 1.5–8 years). One patient underwent partial resection and four had excisional biopsy. Three patients received multidrug chemotherapy with vincristine, actinomycin-D, and cyclophosphamide. Two patients received chemotherapy plus second surgery and radiation therapy to the pelvis. Group B: Twelve patients with leiomyosarcoma; median age 55 years (range 40–81). Nine patients had localized diseases, one had extensive local disease, and two patients had distant metastases to the liver and lung. Ten patients underwent surgery (eight total abdominal hysterectomy [TAH]) and exploratory laparotomy with excisional biopsy. Group C: Six patients with rhabdomyosarcoma; median age 40 years (range 20–45 years). Four patients with localized disease of the uterus underwent TAH and bilateral salpingo-oophorectomy (BSO). Two patients with localized disease of the vulva had vulvectomy followed by chemotherapy (vincristine, cyclophosphamide, actinomycin–D). Detailed demographic, local control, and survival data will be presented.

A CLINICAL STUDY OF OSTEOSARCOMA IN ALEXANDRIA, AF Eid, E Abbassy, A Zaki, Faculty of Medicine, University of Alexandria, Alexandria, Egypt, IH Abu Shamala, Al-Midhnab General Hospital, Al-Gassim

A total of 116 cases of malignant bone tumors admitted to El Hadra Orthopedic and Traumatology University Hospital, Alexandria, Egypt, during five years were analyzed for the important clinical features and the survival rate and factors influencing it. The results of this work showed: osteosarcoma was the most common primary malignant bone tumor (51.7%). Its greatest incidence was in the younger age groups. Seventy percent of cases occur within the second decade of life and 81.6% were younger than 20 years of age. The mean age was 16.3% years. The male female ratio was 1.9:1. The preferential site was the metaphysis of a long bone. Ninety-five percent of cases occur around the knee. The femur, in particular, was affected in 45% of the cases. The minimal incidence rate (MIR) of osteosarcoma in Alexandria was 4.74/million per year. There was no statistical significance between the probability of death after osteosarcoma and the age, sex of patient, or site of tumor. Osteosarcoma was a very malignant tumor with a poor prognosis and a survival period of approximately 20.4 months. The probabilities for a patient with osteosarcoma to live one year, two years, or three years after treatment were 0.95 (95%), 0.69 (69%), and 0.55 (55%), respectively.

HLA, -B AND -C SPECIFICITIES IN OSTEOSARCOMA IN THE EGYPTIAN POPULATION, AF Eid, M El-Sawy, E El-Abbassy, Faculty of Medicine, University of Alexandria, Alexandria, Egypt; IH Abu-Shamalah, Al-Midhnab General Hospital, Al-Midhnab, Al-Gassim

The linkage of osteosarcoma to immunological consequences by some authors raised the importance to determine the HLA-A, -B, and -C specificities in these patients in the Egyptian population. The study has been carried out on 20 patients with osteosarcoma and 30 healthy control subjects matched for age and sex as patients included in this study. The results of the present work showed a trend to increase frequency of HLA-A2, a statistically increased frequency of HLA-A2/A9 combination with HLA-Cw4 specificity; while HLA-Aw 23 antigen has been completely absent in all cases of osteosarcoma. These findings can be considered in harmony with the view of a genetic contribution, particularly through the HLA system, to the pathogenesis of the disease.

SOFT TISSUE SARCOMA: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE EXPERIENCE, A Ezzat, R Wierzbicki, F Khalifa, A Bedikian, AA El-Warith, R Sabbah, K Sackey, H Schultz, S El-Akkad, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, T Amin, M Abdulkareem, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and 1991, a total of 497 patients with the diagnosis of soft tissue sarcoma (STS) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). The median age was 32 years (range 4 days to 90 days) and male to female ratio 1.2:1. Seventy (70%) presented with a mass, 28% with pain, 7% with upper respiratory tract symptoms, 5% with urinary symptoms, and 7.5% with constitutional symptoms (fever and weight loss). Duration of symptoms ranged from one day to 72 months, median five months. The tumor was most often localized in the extremity (42%), trunkal (36.4%), head and neck (16.3%), and retroperitoneal (5.3%). The most common histological subtypes were rhabdomyosarcoma (20.3%), malignant fibrous histiocytosis (15.3%), leiomyosarcoma (11%), fibrosarcoma (10.5%), liposarcoma (9%), and spindle cell sarcoma (9%). Tumor was graded in 183/497: 10% Grade I, 42% Grade II, and 42% Grade III. At presentation, 78.5% had localized disease and 21.5% had metastases: 58% (lungs), 26% (lymph nodes), 18% (liver), 16% (bones), 8% (brain), and 6% other sites. Patients were treated using multidisciplinary approach which included surgery, +/– radiation therapy, +/– chemotherapy (vincristine, cyclophosphamide +/– actinomycin-D, +/– adriamycin). Using the above approach, the overall response rate for the whole group, localized and metastatic, was 63%. The three and five year overall survival, excluding other causes of death, was 34% and 18.2%, respectively. A total of one hundred forty-nine patients were lost to follow-up.

CLINICOPATHOLOGICAL STUDY OF CYSTOSARCOMA PHYLLODES (CSP) SEEN AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC), A Ezzat, R Wierzbicki, AA El-Warith, A Ali, T Amin, N Abdulkareem, M El-Senoussi, V Saleh, King Faisal Specialist Hospital and Research Centre, Riyadh

Cystosarcoma phyllodes (CSP) is a rare tumor of fibroepithelial tissue of the breast. Between 1980 and 1990, 12 female patients with CSP were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). All were Saudi nationals. Five patients (42%) were from the South, and a similar number were from the Central region of the Kingdom; median age of 45 years (range 16–65). Seven patients (58%) were premenopausal, four of whom were single. Of the five post-menopausal patients, two were single while the other two were infertile. All patients presented with breast mass which was centrally located in six (50%). The median duration of symptoms was 15 months. The mass was more than 10 cm in seven patients (58%). At the time of diagnosis no axillary lymph node involvement or distant metastases were reported. Only one patient was referred to KFSH&RC with metastatic disease involving bone. Surgery was the modality of treatment for locoregional control. Ten patients (83%) had mastectomy, while the other two patients had conservative surgery. Pathological malignant CSP was confirmed in all cases. Of tumors assayed for ERP/PR, none were positive. After a median follow-up of 17 months, three patients relapsed (6, 11 and 19 months, respectively). One patient had a local recurrence, contralateral cystosarcoma phyllodes, and lung metastases, while the other two had lung and bony metastases. The projected five year survival for all patients is 83%. This limited data supports that cystosarcoma phyllodes has a different natural history than other epithelial tumors of the breast.

EWING'S SARCOMA, V Fornasier, Wellesley Hospital, Toronto, Canada

Ewing's sarcoma (ES) is a highly malignant tumor which has generally been regarded as a "malignant round cell tumor". As part of the differential diagnosis that is generally applied to Ewing's sarcoma, one includes neuroblastoma, malignant lymphoma, leukemia (chloroma), anaplastic small cell carcinoma, undifferentiated multiple myeloma, and primitive neuroectodermal tumor. Ewing's sarcoma is sometimes referred to by clinicians as the "Great Imitator". This is a recognition of the fact that it is a rapidly growing tumor that is subject to extensive necrosis. Thus, at the time of biopsy, the surgeon may encounter a soft semi-liquid mass that will "ooze" once the surrounding tissues are opened and give the appearance of pus. As the above description implies, Ewing's sarcoma is characterized microscopically by sheets of compact cells which are closely packed together with no recognizable intercellular matrix. The Ewing's cells have very little cohesion and percolate into the surrounding tissues as individual cells. An important feature to remember is that although the tumor cells produce no matrix, they can stimulate periosteal reaction. Often there is an attempt at subclassification of Ewing's sarcoma cells into whether they are large cell or small cell in type. Unfortunately, this can be a very difficult issue to deal with because the size of the cell and its overall appearance is very much dependent on fixation and tissue processing. A characteristic, but not necessarily diagnostic feature described by Schajowicz, was the presence of an abundance of demonstrable glycogen in the cytoplasm of Ewing's sarcoma cells. For the time being, clinical, radiological imaging, and histological correlations will be essential to assure a correct diagnosis of Ewing's sarcoma.

OSTEOSARCOMA: A PHILOSOPHY, V Fornasier, Wellesley Hospital, Toronto, Canada

Osteosarcoma is a malignant tumor arising in mesenchymal cells in which the cells differentiate to deposit bone matrix which may or may not be mineralized. Such tumors may have a variety of cellular patterns ranging in size, shape, and staining characteristics. The definitive feature identifying a sarcoma as an osteosarcoma is the deposition of osteoid which may or may not be mineralized. Osteosarcoma can be divided into three broad categories: the lytic pattern, osteoclerotic pattern, and a combination of osteolysis and osteosclerosis. These can be divided into four general groups: (1) central, (2) on the surface of the bone, (3) secondary, and (4) other. The central osteosarcoma is usually divided into the "classic" grouping of fibroblastic, osteoblastic, and chondroblastic osteosarcomas. The osteosarcomata arising on the surface of the bone are generally classified into parosteal, the periosteal and the high grade on the surface of the bone types. The third category of osteosarcoma is that arising from pre-existing benign conditions, or as a result of injury to the tissue. This will include the osteosarcomata arising in Paget's disease as well as tumors arising in the bone that have been irradiated. The actual assessment of therapeutic effect has been particularly difficult, variable, and often confusing. Often, it is impossible for the pathologist to determine if the necrosis present is due to spontaneous tumor necrosis in a growing tumor or whether it is due to therapy.

SOFT TISSUE SARCOMATA: A PREVIEW, V Fornasier, Wellesley Hospital, Toronto, Canada

Soft tissue sarcomata are malignant neoplasms of soft extraskeletal tissues. They have an extremely variable pattern and degree of differentiation and may have only partial or incomplete resemblance to the "tissue of origin". Traditionally, tumors are classified on a histogenetic basis. Current concepts of neoplasia have suggested that the oncogenetic process is best regarded as a process of adaptation. Soft tissue sarcoma can differentiate toward a single cell type (e.g. fibrosarcoma), a two cell type (e.g. synovial sarcoma), or a multiple cell type (e.g. mesenchymona). For this reason, it is important to accept the changing concepts of oncogenesis, but for practical purposes in the clinical setting to arrive at a system of classification that reflects the probable clinical behavior of the lesion. Grading is a means of assessing biologic behavior. The clinician will use grading as part of the overall assessment of a patient in the process of staging the disease. Unfortunately, over the years grading has been particularly inconsistent in subjective assessment of selected criteria. Five of the criteria applied provided statistical significance and together these were found to be most clearly discriminatory in predicting biological behavior. These were: (1) cellularity and pleomorphism, (2) pattern of invasion at the margin of tumors, (3) mitotic rate, (4) presence of necrosis in tumor, and (5) evidence of vascular invasion or damage. Within each of the five criteria, a semi-quantitative value was ascribed from 0–3 so that the five criteria could provide a range of rating from 0–15. It was discovered that any sarcoma regardless of the histologic type with a rating of ten or more was associated with death of the patient from his tumor, while any scoring of five or less was associated with long-term survival. The pathologist's assessment of soft tissue sarcoma cannot be carried out in isolation of clinical and cardiologic findings.

ADJUVANT EPIRUBICIN AND PLATINUM IN HIGH GRADE NON-METASTATIC OSTEOSARCOMA OF THE EXTREMITY, R Hamza MH Hussein, S Eissa, S Abdel Hadi, O El-Tannir, A El-Hadad, SH Abouel Waga, AM Zamzam, National Cancer Institute, Cairo University, Cairo, Egypt

Since January 1990 a non-randomized, one arm trial for the treatment of non-metastatic high grade osteosarcoma (0.8) of the extremity after radical surgery was started at the Pediatric Department of the National Cancer Institute (NCI), Cairo. Adjuvant chemotherapeutic regimen consisted of epirubicin 40 mg/m(2) d1–d3 and platamine 90 mg/m(2) dl (Farmatalia Carlo Erba) repeated three to four weeks as tolerated for a total of six cycles. This study was designed to test the feasibility, toxicity, and the effects of this regimen on the metastasis-free survival (MFS). Fourteen patients completed their six cycles in August 1991. There were eight males and six females, whose ages ranged between 9–19 years (mean 14 years). The most common primary site was the femur (11/140). The actuarial one year MFS was 78+12%. The toxity was tolerable with no life-threatening complications. Although our results are handicapped by a small sample size and a short follow-up period, a number of indicators could be elicited if compared with another matched group of patients (N = 20) presented during the years 1988–1989. This matched group was managed with radical surgery alone. The MFS of this control group was 20% at one year. The difference between both groups was statistically significant. This trial is still going on with entry of more patients hoping for improving the MFS of patients with this aggressive tumor.

MRI OF PELVIC RHABDOMYOSARCOMA IN CHILDREN, C Hugosson, K Sackey, King Faisal Specialist Hospital and Research Centre, Riyadh

The value of magnetic resonance imaging (MRI) was studied in 11 children, between four months and seven years of age, with pelvic rhabdomyosarcoma. Spin echo technique with T1-weighted coronal and sagittal and T2-weighted axial images were performed in all patients; additional images were taken if necessary. In five patients, Gadolinium-DTPA was given. The findings of MRI were compared with the findings of ultrasonography (US) and computed tomography (CT). MRI demonstrated superior delineation of surrounding structures. The signal intensity at T1-weighted images was intermediate, uniform and similar to muscle, a pattern not regularly seen in other solid pelvic tumors in children. Neither US or CT showed any specific echogenicity or attenuation. Changes in size during treatment was seen equal by US, CT, and MRI. Changes in signal intensity during treatment occurred in six out of eight children who had repeated examinations. Marked enhancement of the tumor with Gadolinium-DTPA was demonstrated in one child, which was probably related to the treatment. MRI offers high soft tissue contrast resolution and a capacity for multidirectional imaging and thus, appears superior to US and CT for pre-treatment and pre-surgery assessment of pelvic rhabdomyosarcoma in children. MRI may also offer valuable information on qualitative changes resulting from treatment with radiation and chemotherapy.

RHABDOMYOSARCOMA IN CHILDREN: CLINICAL PRESENTATION AND RESPONSE TO COMBINED MODALITY TREATMENT, MH Hussien, MS Zaghloul, MR Hamza, S El-Badawi, S Abdel Hadi, O El-Tannir, A El-Hadad, A Abdel Wahab, M Abdel Kader, National Cancer Institute, Cairo University, Cairo, and Suez Canal University, Egypt

During the period of 1980–1988 a total of 104 children with rhabdomyosarcoma were presented to the National Cancer Institute (NCI). Their ages ranged between eight months and 16 years with a mean age of five years and median of 5.6 years. The male to female ratio was 1.5:1. The genitourinary and head and neck sites were the most frequent sites of presentation followed by extremities and trunk, while retroperitoneal rhabdomyosarcoma was encountered in three patients only. All patients were staged according to the Intergroups Rhabdomyosarcoma (IRS) grouping system. Most of the patients (58%), were staged as group III while children staged as groups I and II did not exceed 7% and 35%, respectively. The pathology was mostly embryonal (82.5%) followed by alveolar (12.5%) and pleomorphic (5%). Children were treated with surgery (biopsy or complete excision) followed by chemotherapy (VAC alternating with VAD) for one year to group I and two years for the most advanced groups. Radiotherapy was applied to all patients more than group I either before or concomitant with chemotherapy. The five-year disease-free survival (DFS) for all patients was 45.5%. The DFS was affected by stage, pathology, and site of presentation. Group III patients had five-year DFS (25%) which was much less than in groups I and II (100% and 62.5%, respectively). The DFS was lower for the alveolar pathology (33%) compared to the nonalveolar one (50%). Among all sites of presentation retroperitoneal and trunk rhabdomyosarcoma had the worst prognosis.

RHABDOMYOSARCOMA: KING FAISAL SPECIALIST HOSPITAL (KFSH&RC) EXPERIENCE: F Khalifa, K Sackey, R Sabbah, H Schultz, R Wierzbicki, A Ezzat, S Ahmed, P McArthur, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and 1991, a total of 100 patients with the diagnosis of rhabdomyosarcoma were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). The median age was five years (range four days to 90 years), and male to female ratio was 1.8:1. Fifty-nine percent presented with a mass, 19% with urinary symptoms, 11% with pain, and 10% with upper respiratory tract symptoms. Duration of symptoms ranged from one day to 24 months (median 2½ months). The most common location was the head 37%, genitourinary 34%, and extremity 11%. Histology, 49% embryonal, 8% pleomorphic, 1% alveolar, and 42% rhabdomyosarcoma unclassified. Tumor was graded in only 17 cases, one grade I, three grade II, and 13 grade III. At presentation, 84% had localized disease and 16% had metastases, 37.5% (lymph nodes), 25% (bones), 25% (lung), 6.25% (brain), and 6.25% (skin). Patients were treated using multidisciplinary approach which included surgery +/- radiation therapy, +/- chemotherapy (vincristine, cyclophosphamide, +/- actinomycin-D, +/- adriamycin). Patients with localized disease had a remission rate of 76% (64/84), with 51% in complete remission (CR), and 25% in partial remission (PR), with a median disease-free survival (DFS) of 24 months (range 1–132 months). The remission rate for patients with metastatic disease was 68.8% (11/16); 25% CR, and 43.8% PR, with a median DFS of 11 months (range 6–89 months). The overall response rate for the whole group (localized and metastatic) was 75%, 47% CR, and 28% PR. The two and five-year survival was 37% and 10.5%, respectively. Twenty-three patients were lost to follow-up.

EWING'S SARCOMA: RKH EXPERIENCE, OM Koreich, Armed Forces Hospital, Riyadh

Ewing's sarcoma (ES) is a relatively rare small cell tumor that usually occurs in the bone and presents most frequently in the second decade of life. Prior to the development of chemotherapy, approximately 20–40% of all patients were cured. Current studies are more encouraging. The location of the primary site of the tumor and the extent of disease are the most important prognostic factors. However, the pathologic characteristics of the tumor, the size, and soft tissue extension of the primary, and serum LDH levels may also be important prognostic variables. At least 90% of patients with apparently localized disease at diagnosis have occult metastatic disease. Thus, the successful treatment of Ewing's sarcoma requires the use of multi-drug chemotherapy in addition to radiation therapy and/or surgical therapy to the primary tumor. A total of 44 patients were treated at the Riyadh Armed Forces Hospital with chemotherapy including vincristine, adriamycin or epirubicin, cyclophosphamide, and dactinomycin (VACA or VECA) combined with radiation therapy and/or surgery. Twenty-one patients were over the age of 15 years, with two over the age of 50 years. At presentation, 12 patients had widespread metastatic disease. There were 12 patients with tumors arising from proximal extremity primaries, seven patients from the pelvis/sacrum, and five from the ribs. These two groups have relatively poor results of therapy. There were 16 patients with distal extremity primaries, and four extraskeletal primaries. The results of treatment and overall survival of this group of patients will be presented. The different prognostic factors including site, extent of disease, serum LDH, and chemotherapy intensity will be reviewed with recommendations of future treatment programs in Saudi Arabia.

OSTEOGENIC SARCOMA OF THE UPPER AND LOWER JAW: KFSH EXPERIENCE, Z Mahasin, KM Taibah, M Abuzeid, H Schultz, S El-Akkad, King Faisal Specialist Hospital and Research Centre, Riyadh

The medical records of six patients with osteogenic sarcoma (OS) of the mandible and maxilla treated at King Faisal Specialist Hospital and Research Centre (KFSH&RC) between 1980 and 1991 were reviewed. The patients ages ranged from 11 to 80 years of age with a median of 32 years. There were three male and three female patients (ratio 1:1). The follow-up period ranged from one month to 35 months. The mandible was the primary site in four cases and two cases presented in the maxilla. Pain and swelling, the most common presenting complaints, were noted two to three months prior to seeking medical attention. Two patients were treated with radical surgery/radiation therapy only. One patient was lost to follow-up shortly after the completion radiation therapy. The other patient had a recurrence at the primary site after five months which necessitated another excision plus more radiation therapy. This patient was free of disease for seven months after which he became lost to follow-up. Two patients were treated with radiation therapy alone died within one to five months of the disease. One patient treated with chemotherapy alone developed pulmonary metastasis and died within five months, while primary disease showed no response to treatment. One patient treated with pre- and postoperative chemotherapy (multiple courses) had radical surgery (hemimandibulectomy). This patient remained free of disease for 35 months and is still doing well on follow-up. We concluded that osteogenic sarcoma of the mandible and maxilla is an aggressive tumor which has a high rate of recurrence at the primary site and of distant metastasis. From this series, and from published experiences involving the head and neck as well as extremities, osteogenic sarcoma of head and neck should be managed aggressively with multimodality therapy.

CHONDROSARCOMA AND OSTEOSARCOMA OF THE MANDIBLE, SH Mahmouod, Billasmar

The explosion of scientific knowledge and technology which has occurred within the past few decades has reached out to leave its impact on all branches of the healing disciplines, including oral pathology, particularly the study of tumors of the oral cavity. Until recent years, chondrosarcoma was indiscriminantly grouped with osteosarcoma, but careful review of clinical data has indicated the need for their definite separation. The aim of this study was to evaluate the nature and frequency of chondrosarcoma and osteosarcoma of the mandible and to identify the specific histological and clinical differentiation of these malignant neoplasms to avoid misinterpretation as symptoms of an inflammatory process. A group of seven patients who developed chondrosarcoma (two cases) and osteosarcoma (five cases) of the mandible are presented. The most common presenting symptoms of the patients are swelling of the involved area producing facial deformity and pain, followed by loose teeth, parasthesia, toothache, and bleeding. The median age of the patients at the time of appearance of the first related symptoms was about 27 years and there was a predilection for occurrence in males. Surprisingly, in all cases, there was no proceeding history of trauma or of Paget's disease.

SYNOVIAL SARCOMA OF THE TONGUE: REPORT OF A CASE, P McArthur, B Hainau, P Smith, King Faisal Specialist Hospital and Research Centre, Riyadh

In August 1989, a 21-year-old Saudi male presented to the King Faisal Specialist Hospital and Research Centre (KFSH&RC) with a six-month history of dysphagia and a mass in the oral cavity and neck. Biopsy of the floor of the mouth proved to be a monophasic synovial sarcoma. The mass replaced most of the tongue and floor of the mouth, extending into the left parapharyngeal space in the neck. No regional or distant disease was noted. In October 1989, a subtotal glossectomy, partial mandibulectomy, excision of floor of mouth, and radical neck dissection was performed, with reconstruction with two titanium custom plates and pectoralis myocutaneous flap. The tumor was described as a lobulated solid tumor measuring 8 × 4 × 4 cm. All surgical margins were clear. In June 1990, the titanium plates fractured and were replaced by an iliac crest bone graft. In December 1990, a large parapharyngeal recurrence and pulmonary metastasis was noted. Chemotherapy was begun in August 1991 when the patient became symptomatic. As of December 1991, the patient remains symptomatic with no apparent progression of the disease. This is the eighth case of synovial sarcoma of the tongue reported. Less than 30 cases of the head and neck have been documented. The five and ten year survival rates are poor, although some authors have concluded that prognosis is improved with postoperative radiotherapy. We have observed from this case that despite wide surgical margins, both local and distant recurrence can occur. In the future, adjunctive therapy might be considered even though results of similar cases remain anectodal.

LIMB SALVAGE IN SAUDI ARABIA, PG Moreau, King Faisal Specialist Hospital and Research Centre, Riyadh

The surgical treatment of bone and soft-tissue sarcomas has changed radically over the past decade. Before 1980, limb salvage surgery was considered only for small low-grade lesions with minimal extraosseous extension. These were most commonly parosteal sarcomas and low-grade chondrosarcomas. All other sarcomas were treated by amputation. The only area of controversy at that time was the level of amputation. A comparative study by the Musculoskeletal Tumor Society reviewing osteogenic sarcoma of the distal femur showed that hip disarticulation (radial resection) did no better than above knee amputation (wide excision). This important observation helped usher in the era of limb salvage surgery. Currently, most extremity sarcomas are treated by limb salvage procedures. Only those of very large proportions or associated with pathological fractures are treated primarily by amputation. The ability to perform a wide excision with reconstruction is due largely to the improvement in imaging studies and chemotherapy. Computed tomography (CT) and magnetic resonance imaging (MRI) have been reliable in showing the extent of the tumor and their relationships with surrounding normal structures, especially the vessels and nerves. Preoperative chemotherapy in a responsive tumor can shrink the lesion to a resectable size, as well as being a prognostic indicator. There are special problems regarding limb salvage surgery performed in Saudi Arabia. Many of our tumors have been neglected, and can be of considerable size. Custom-made prostheses are not readily available, nor are allografts. The use of stacked intramedullary rods with cement has been invaluable in creating an "instant arthrodesis" of the knee for distal femoral and proximal tibial lesions. Tumors of the proximal humerus have been treated with long-stem Neer replacements with cement augmentation. Modular prostheses are now currently available for limb salvage, although our experience with these is short and still uncertain.

DIRECT SEEDING OF OSTEOGENIC SARCOMA TO THE DONOR BONE-GRAFT SITE, A Mukherjee, A Shah, S Agarwal, SM Kadhi, King Faisal Specialist Hospital and Research Centre, Riyadh

Osteogenic sarcoma (OS) is one of the most frequent primary malignant tumors of bone. Males in their second decade appear high in the susceptible list of this most unfortunate disease. Any doubt in diagnosis or inadequate treatment can have a disastrous effect for the individual patient. We report six cases of osteogenic sarcoma treated by intralesional curettage and bone-grafting. In all these cases there were diagnostic errors leading to such procedures. All patients had recurrence of tumor at the primary site, and one presented with histologically proven osteosarcoma of the donor graft site, namely the iliac crest. As far as we are aware, there has been no report in the literature of patients developing the same primary bone tumor at the donor graft site. We strongly feel that this patient had direct seeding of the malignant cells due to surgical contamination. We, therefore, recommend that even for benign-looking tumors, all bone-grafting procedures be performed with utmost care. To stress the point further, we feel all bone-grafts should be obtained prior to commencing surgery at the primary tumor site. This will avoid surgical contamination.

EWING'S SARCOMA: TREATMENT RESULTS AND PATTERN OF FAILURE, M El-Naggar, H Abdel Baki, H Akoush, S El-Badawy, R Hamza, National Cancer Institute, Cairo, Egypt

This report includes 85 patients with Ewing's sarcoma (ES) seen during the period 1976-1985. Out of 85 patients, 50 were treated according to a combined chemo-radiotherapy protocol, but the remaining 35 patients received individualized treatment. The protocol involved radiotherapy to the entire involved bone with a dose of 50–65 Gy/5–7 week. Chemotherapy was given concomitantly with radiotherapy and consisted of either a VAC or VAC-Adriamycin regime from one to two years. A minimum follow-up period of two years is available for the protocol patients with a maximum of ten years. The two year disease-free survival amounted to 40% (20/50). Some correlation could be demonstrated between disease-free survival and the duration of chemotherapy. Survival amounted to 46% (12/26) in patients receiving 12 cycles and 33% (8/24) for 6–11 cycles. In protocol patients, recurrence amounted to 18% (9/50). This is apparently related to the large volume of the primary tumor at the time of presentation which was greater than 1000 ML(3) in 70% of patients. Distant metastases was encountered in 60% of patients. In conclusion, an aggressive chemo-radiotherapy protocol is needed in the treatment of Ewing's sarcoma with (1) high dose radiotherapy to the entire bone, and (2) chemotherapy extended to more than one year.

ONCOLOGY DEPARTMENT ORGANIZATION FOR CANCER CARE, A Padmos, King Faisal Specialist Hospital and Research Centre, Riyadh

Demand for cancer diagnostic, therapeutic supportive, and palliative services in Saudi Arabia far exceeds current supply. The Oncology Department of King Faisal Specialist Hospital and Research Centre (KFSH&RC) provides the largest concentration of oncology resources in the region and embraces the broad objectives of service to patients, professionals and the public and research to improve and expand cost-efficient care. The department has the responsibility to communicate effectively with all participants in the matrix of care providers and consumers. Multi-modality therapeutic services are provided in the radiotherapy and outpatient oncology clinics. Specialized supportive treatment is given in nursing units such as the bone marrow transplant and medical oncology wards. Education programs strive to improve the quality of care. Specialty training for fellows and post qualification training of medical and pediatric residents is conducted along with contributions to organized professional and paramedical training programs. The recently opened clinical research unit and expanded tumor registry support increasing clinical trial and research protocol activities. Standardized institutional approaches to the investigational therapy of cancer by diagnosis and site improves service to patients, education of staff, and stimulates research projects. Departmental quality assurance programs audit and improve patient care. Considerable effort is devoted to improving communication between department staff, outside physicians, and hospitals to promote cooperative care of oncology patients in their local setting.

RHABDOMYOSARCOMA IN CHILDREN (RMS): PROVEN AND UNPROVEN FACTORS INFLUENCING CHOICE OF THERAPY, K Sackey, King Faisal Specialist Hospital and Research Centre, Riyadh

With the use of multi-modality treatment consisting of chemotherapy, +/– surgery, and +/– radiation therapy, the DFS of RMS at three years is 90% (GpI), 80% (GpII), 70% (GpIII), and 20% (Group IV). Therapy has been tailored, conventionally influenced by three prognostic factors; (1) group or stage, (2) site of primary, and (3) histology. Data now accumulating from studies in childhood RMS and other solid tumors indicate that events that precede the appearance of a tumor may help even better in selecting specific therapy for different populations of patients. These emerging factors include; (1) DNA profiles–aneuploidy = better prognosis, and (2) cytogenetics t(2:13)(q37:q14) = poorer prognosis. Studies from Intergroup Rhabdomyosarcoma (IRS) indicate that 65% of patients are in Group III/IV. Most lesions (in Group III) are however in locations that generally do not subject themselves to resection, e.g. head and neck. In the developing world unresectability is more related to size than location. Our patients also have a longer symptom to diagnosis interval, thus predisposing to clinically detectable as well as undetectable metasis at diagnosis. Our patients are also sicker, more anemic, and nutritionally compromised, hence limiting our aggressiveness to treatment. A further limitation is support facilities, more specifically bed availability. Until our support facilities improve and patients present earlier and in better physical condition, it would be most unwise to indiscriminantly adopt aggressive western-type treatment regimens. One has no choice but to use milder effective, albeit inferior therapy to save a majority of those salvageable, rather than use aggressive therapy and lose a majority.

CLEAR CELL SARCOMA OF THE KIDNEY (CCSK) IN CHILDREN < 14 YEARS: CLINICAL FEATURES AND RX RESULTS OVER 9 YEARS, K Sackey, M Akhtar, C Hugosson, SJ Crankson, S Ahmed, King Faisal Specialist Hospital and Research Centre, Riyadh

From March 1982 to September 1991, a total of 100 children with primary renal neoplasms (PRN) were seen at King Faisal Specialist Hospital and Research Centre (KFSH&RC). Of these, 13 (13%) had CCSK. Male:female ratio = 8:5, (R):(L) = 9:4. Ages were seven months to seven years, median [M] = 3 years. Symptoms were abdominal mass (10, abdominal pain (3), hematuria (3), abdominal distention (3), and occipital mass (1). Duration of symptoms was ten days to one year [M = 1 month]. Stage (S) as per NWTS were SI(5), SII(5), and SIV(2). Treatment (Rx) consisted of radical nephrectomy (RN) [13/13], radiation ORT [10/13], 2000-400 cGy to primary site, chemotherapy (CT) [11/13] VCR < ACTD, ADRIA × 15 months. One patient refused Rx post RN. One patient was lost to follow-up post RN. Of 11 evaluable patients, one (SIV) showed progressive disease (local and metastatic) at three months (no CT for three months), three (SI, SII, SIV) relapsed (intracranial, spinal, spinal) at 26, 6, 22 months, respectively. Salvage Rx (SRx) consisted of surgery (3/4), CddP (200 mg/m(2) + VP16 (600 mg/m(2) [3/4], RT (2/5). Two patients are free of disease (FOD) at three and 33 months from relapse from the date of diagnosis. Major toxicity was myelosuppression for both CT regimens. In summary, CSSK (1) accounts for 13% of PRN, (2) is more common in males (3) local recurrence can be prevented by radical surgery and RT irrespective of stage, (4) aggressive initial multi-modality Rx may lead to long-term disease free survival (7/11), (5) aggressive Rx with CddP containing regimen can salvage patients after relapse (2/3), and (6) overall DFS for this series is 85% (9/11) for a median of 55 months (9–93 months) from diagnosis.

RHABDOID SARCOMA OF KIDNEYS IN CHILDREN < 14 YEARS: CLINICAL OBSERVATIONS, K Sackey, M Akhtar, C Hugosson, S Ahmed, SJ Crankson, King Faisal Specialist Hospital and Research Centre, Riyadh

Rhabdoid sarcoma (RS) is the rarest of all primary renal neoplasms (PRN). During an 18 year period, only 79 cases were identified in the National Wilms Tumor Study, USA (NWTS) [1.8%]. From August 1982 to September 1991 (nine years), six patients with RS were identified out of 100 with PRN seen at King Faisal Specialist Hospital and Research Centre (KFSH&RC) [6%], male:female = 4:2. Ages at first presentation of symptoms and signs (S/S) were 1 day, 1 day, 4 weeks, 8½ years, 12 years, 13 years, respectively. Symptoms and signs were abdominal mass (2), abdominal pain (3), hematuria (3), and abnormal eye (1). Stages (S) were; SI(1) SIII(1), and SIV(IV) according to NWTS. Five patients had unilateral disease and one patient bilateral disease. Evaluation consisted of US + CT + MRI brain, x-ray CT chest, bone scan, BMA + biopsy. Rx consisted of radical nephrectomy (RN) [5/6] and RT [2/6]. Chemotherapy (CH) varied: Group 1 (< 1990); VCR containing regimen (VCR/ACTD, VCR/ACTD/ADR, VCR/CYCLO/ADR). Group 2 (> 1990), CDDP containing regimen (CDDP/VP16, CDDP/VP126, CDDP/VP16/IFOSF). The results were: Group 1 – dead 1 m, PD 3 m, FOD 55 m (two thoracotomies); Group 2 – dead 1 m (CH toxicity), FOC 11 m + PD 12 m, FOD 4 m + relapse. In summary, (1) RS is a very aggressive disease (short duration of S/S, advanced disease at diagnosis). Extremely poor prognosis, (2) two peaks, infancy and adolescence: higher frequency (6%), at KFSH&RC, (3) recognition of this entity as different from Wilms tumor (WT), is important because of a different natural history; e.g., brain tumors, metastases and lack of response to CH used for WT, and (4) ideal Rx combination is still elusive, but includes radical surgery +/- CDDP =/RT.

MULTIDISCIPLINARY MANAGEMENT OF SARCOMA PATIENTS IN THE OUTPATIENT CLINIC, V Saleh, R Altese, King Faisal Specialist Hospital and Research Centre, Riyadh

Surgery has been the cornerstone of treatment of patients with sarcomas. Evidently, systemic treatment is required to enhance curability. A Combined Sarcoma Clinic (CSC) is needed to facilitate decision making by representatives of Surgery, Radiation, and Medical Oncology. In May 1990, a Combined Sarcoma Clinic was started in the Outpatient Oncology Clinic at King Faisal Specialist Hospital and Research Centre (KFSH&RC). The numbers of patients have steadily increased, and currently as many as four new patients and 18 follow-up patients are seen weekly in each clinic session. The clinic is operated by a combined team of Medical Oncologist, Radiation Oncologist, Orthopedic Surgeon, and Oncology Nurses. All sarcoma patients are fully screened, examined by the treating consultant who formulates a treatment plan with necessary exchange of information and opinions with the other members of the team. The patients benefit not only from the multidisciplinary approach but also from the continuity of care provided by this clinic. Hopefully, the CSC will serve as a model for combined multidisciplinary clinics to be developed in other diagnostic categories for patients of the Oncology Department at KFSH&RC.

AGGRESSIVE FIBROMATOSIS CLINICAL PRESENTATION AND MANAGEMENT: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE EXPERIENCE, M El-Senoussi, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1979 and 1990, a total of 30 patients with the diagnosis of aggressive fibromatosis were referred to the King Faisal Specialist Hospital and Research Centre (KFSH&RC). Seventy percent were Saudi and 57% were female. The mean age at the start of symptoms was 26 years with 27% younger than age 15. The head and neck regions were the primary site in 23%, the shoulders in 10%, the upper and lower limbs in 37%, the thoracic region in 20%, and the abdominal and pelvic regions in 17%. In a newly born, the disease was multicentric. The mean delay between appearance of symptoms and definitive diagnosis was seven months, while the mean delay between diagnosis and start of therapy was seven weeks. Twenty percent of patients were treated only by surgery, and 73% by surgery and radiotherapy. One patient was treated by radiotherapy only. One patient discharged herself after diagnostic biopsy. Thirty-nine percent had one surgical attempt, 25% had two surgical attempts, 21% had three surgical attempts, and 14% had four or more surgical attempts. In 68% the surgery was partial excision, and in 32%, the surgery was of radical intention. Six patients were not evaluable for different reasons. Twenty-four evaluable patients had follow-up which varied between 11–125 months, respectively, with a mean of 58 months. Eight percent had no evidence of disease, 63% with stable disease, and 29% with local and/or marginal disease progression. Three patients are alive with complications and one patient expired after ten years from complications while having progressive disease.

EPIRUBICIN, IFOSFAMIDE AND MESNA FOR ADVANCED SOFT TISSUE SARCOMA, M El-Serafi, NG El-Mawla, R Hamza, S Essa, National Cancer Institute, Cairo, Egypt

Sixteen patients with metastatic, recurrent or advanced soft tissue sarcoma who had received no previous chemotherapy had been treated by combination of epirubicin 90 mg/m (2) and ifosfamide 5 gm/m (2) with 25% mesna as one day treatment. Cycles were given every three weeks. There were eight males and females with age (20–65), average 41.4. Performance status was 70–70 KS. Pathology types included: fibrosarcoma and malignant fibrous histocytoma, four patients in each type. Rhabdomyosarcoma and mixoliposarcoma, three patient type. Liposarcoma and leiomyosarcoma one patient each. Toxicity was acceptable with grade 3 nausea and vomiting in all patients. Leucopenia (1.0–1.9) 6/16-alopecia all patients. Microscopic hematuria 6/16-elevation of liver enzymes in six patients. There was no evidence of cardiotoxicity as evaluated by echocardiogram even in patients who received > 1000 mg epirubicin (eight patients) with an average maximum dose of 1488 mg. The response rate was 50% with 6.2% CR for 12+ months. The duration of PR was five months (4–7). Epirubicin and ifosfamide are effective. Frontline chemotherapy in patients with soft tissue sarcoma with acceptable to toxicity. This study was performed under a grant from Farmitalia Carlo Erba.

THE ROLE OF IMAGING TECHNOLOGY IN SURGICAL RESECTION OF THE BONE TUMOR, A Shah, S Parikh, A Mukherjee, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Surgery, either resection or an amputation, is one of the main modalities for treating malignant bone tumors. The margin of a surgical resection has been traditionally decided by plain radiographs and macroscopic pathology seen by the surgeon during surgery. The role of imaging technology such as bone scan, computed tomography (CT) and magnetic resonance imaging (MRI) is well established in detecting multicentric lesions and metastasis. Recently, imaging techniques have become an important tool in deciding margins and extent of the tumor, delineation of neurovascular bundle and its approximation with the tumor mass. Between 1987 and 1989, 24 patients underwent resection of bone tumors at the King Faisal Specialist Hospital (KFSH&RC) in Riyadh, Saudi Arabia. Bone scan, CT, and MRI imaging techniques were used to decide the surgical margins and location of neurovascular bundles and other important structures. Resected specimens from these patients were examined macro- and microscopically by pathologists for the definitive extent of the tumor. A retrospective tabulation was performed to correlate pathological and radiological findings to measure sensitivity and specificity of the imaging techniques. Early results showed that MRI and CT are fairly accurate in defining tumor mass and neurovascular bundle. It appears that MRI slightly exaggerates the margins while CT scan has more specificity. We suggest that for accurate marginal, wide, or radical resection of the tumor, the noninvasive techniques are very useful and should be included in routine preoperative work-up for the patient with the bone tumor.

RECENT ADVANCES IN SURGERY FOR BONE SARCOMAS, FH Sim, Mayo Clinic, Rochester, Minnesota, USA

The outlook for patients with osteosarcoma has improved dramatically because of recent development in diagnosis and treatment that enable the surgeon to achieve the goals of treatment, namely control the primary lesion, maintenance of function, and long-term survival. In addition to improved imaging modalities to clearly delineate the extent of the lesion, effective neoadjuvant chemotherapy and better techniques of reconstruction have stimulated successful limb salvage procedures. Currently our neoadjuvant chemotherapy program utilizing ifosphamide, adriamycin, methyltrexate, and cisplatin has been effective with a consistently high percentage of tumor necrosis. Moreover from the functional standpoint, the results after limb sparing surgery have been very gratifying. Many potential reconstructive procedures for various situations have been described including osteoarticular allografts, prosthetic replacement, a bioimplant, or an arthrodesis. Therefore today's oncological reconstructive surgeon must be versatile to select a variety of reconstructive options which must be individualized and best suited for particular patients according to the patient's age, lifestyle and vocational needs.

RECENT ADVANCES IN SURGERY FOR SOFT TISSUE SARCOMAS, FH Sim, Mayo Clinic, Rochester, Minnesota, USA

In recent years, advances have been made in earlier recognition and in management of soft tissue sarcomas. These advances include improved clinical pathologic correlation and clinical staging based largely on improved imaging modalities for soft tissue lesions. Moreover, a better understanding of the biology of these tumors has led to an improved concept of what constitutes adequate surgery. In addition, recent advances in surgical adjuvant treatment programs hold promise for better results. Advances in pretreatment assessment included computed tomography, magnetic resonance imaging, and pathologic assessment of the lesion have results in more accurate clinical staging and improved outcome. The Musculoskeletal Tumor Society has proposed definitions of surgical procedures for soft tissue tumors that depend on the anatomic confines of the operation in relation to the site of the tumor. The surgical procedures are described by both the surgical margins and the techniques by which they are accomplished. An intralesional margin is achieved by an incisional biopsy or debulking procedure, where the plan of the resection violates the pseudocapsule and leaves macroscopic disease. A marginal excision is accomplished by en bloc removal, with the plane of resection adjacent to the reactive pseudocapsule, which is likely to leave microscopic disease. With this technique, satellite lesions may be missed. A wide margin is obtained by removal of a cuff of normal tissue beyond the pseudocapsule. A radical margin is achieved by an en bloc removal of the entire compartment. Our present approach for treatment of soft tissue sarcomas at the Mayo Clinic is a combination of preoperative chemotherapy and radiation therapy. Approximately 5000 Cg is given, followed four weeks later by surgical resection of the lesion and catheter implantation for subsequent brachytherapy. This program of managing soft tissue sarcomas has resulted in improved local control with only five out of 65 patients showing signs of local recurrence.

SURGICAL TREATMENT OF EWING'S SARCOMA, FH Sim, Mayo Clinic, Rochester, Minnesota, USA

Ewing's sarcoma is a distinctive small round cell tumor which has been the most lethal of bone tumors. However there has been considerable improvement in recent years in the prognosis for patients with localized Ewing's sarcoma of bone. The survival has improved from a dismal five-year survival of 22% to currently 60–70% in recent reports. This improvement stems largely from the use of aggressive adjuvant chemotherapy. With patients surviving longer, it has become evident that radiation therapy is not always successful in controlling the local disease and in addition may be complicated by considerable morbidity. As a result, recent interest has been expressed in substituting surgical treatment for radiation therapy in selected situations. Presently a team approach is utilized combining all known effective modalities with combinations of chemotherapy, radiation, and surgery. It is anticipated that the role of surgery in the treatment of the primary lesion will be greater as more experience is gained.

RADIATION IN CURRENT MANAGEMENT STRATEGIES FOR EWING'S SARCOMA, H Suit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

There is increased concern as to the most appropriate treatment strategy for the primary Ewing's sarcoma. This has developed in response to the accrual of clinical data which demonstrates two major findings: (1) aggressive multiagent chemotherapy has increased the five year survival rate from a level of =8–10% for treatment by local modalities alone to the current levels of =50–70% (depending upon tumor site and volume), and (2) the incidence of local failure in most recently reported series [chemotherapy and radiation] is 10–30%. That local failure is prejudicial to patient cure is not open to serious question. There have been a series of reports which indicate that Ewing's sarcoma patients treated by chemotherapy, surgery + radiation experience remarkably few local failures and an improvement in disease free survival. There are no data from prospective trials of the impact of surgical resection on local control and survival with comparable local extent of disease in the radiation and surgery groups. In a review of the results at the Massachusetts General Hospital [2] there were no local failures in the operated patients as compared to 34% in the drug + radiation patients. For patients whose tumors were < 8 cm, the five year local control rates were = 90% for both the recent BID protocol and for the historical QD controls (once a day treatment, 1969–1981). However, the local control results for those patients with tumors > 8 cm appear to have been substantially improved by the hyperfractionated/accelerated fractionation protocol relative to the historical controls viz = 85% and 60%, respectively.

SARCOMA OF SOFT TISSUE: MANAGEMENT OF THE PRIMARY LESION IN ADULT PATIENTS BY RADIATION AND SURGERY, H Suit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Results of various treatment protocols are presented with attention given to margin status and wound healing after preoperative radiation. The status of the surgical margin and local control has been assessed in 133 consecutive patients. Five year actuarial local control rates were 94% for all patients; 97% and 78% for - margins and + margins, respectively. For primary sarcomas, local control rates were 100%, 97%, 93% and 100% for margins which were negative at # 1 mm, > 1 mm, undefined or the specimen negative for tumor; for positive margins the result was 80%. Wound healing morbidity was retrospectively analyzed in 202 patients treated with preoperative irradiation and consecutive surgery at the Massachusetts General Hospital. The overall wound complication rate was 37%. One patient died of necrotizing fascitis. In 33 cases, secondary surgery was necessary, including six amputations. Multivariate analyses show significant association with wound morbidity of: lower extremity, increasing age, and boost with interstitial implant. Accelerated fractionation [BID] reached borderline significance. No association was found for: sex, diabetes, hypertension, obesity, tumor size, primary versus recurrent tumor, duration of bed rest post surgery, boost dose, the use of adjuvant chemotherapy. For severe wound complications [requiring secondary surgery] only localization in the lower extremity was significant [$P < 0.001$]. Techniques for managing the wound are considered which are judged likely to contribute to a decrease of the incidence of wound healing delays.

SOFT TISSUE SARCOMA OF PARANASAL SINUSES AND ADVANCED SKULL BASE INVASION, KM Taibah, Z Mahasin, I Kanaan, M Abuzeid, P McArthur, H Schultz, S El-Akkad, King Faisal Specialist Hospital and Research Centre, Riyadh

In general, soft tissue sarcomas which originate in the nose and paranasal sinuses are rare, although they can occur in any age group; the peak incidence is in the third to fifth decades of life. We are reporting on advanced cases of different types of sarcoma of paranasal sinuses which involve the skull base with intracranial extension. From 1980–1991 we report 30 cases of different types of nasal and paranasal sinuses sarcoma. Four of the cases had intracranial extension and will be discussed. One of the cases, a chondrosarcoma of paranasal sinus with complete blindness, extended intracranially to the brainstem. This patient had bifrontal craniotomy and transfrontal subtotal removal of the tumor by using microsurgical technique and reconstruction of the skull bed defect with soft stainless steel mesh duraplasty, followed by radiotherapy treatment. At one year follow-up, this patient remains asymptomatic with adequate control of the disease. The second case, a Ewing's sarcoma of the ethmoid sinuses, had intracranial subfrontal extension. This patient had bilateral craniotomy and complete removal of the tumor, followed by chemotherapy and radiotherapy. At two years post treatment, he is tumor and symptom-free. Of the last two cases of fibrosarcoma of ethmoid sinuses, one was radiated in another country and was unresectable when presented to us and the patient died from his disease. The second case with cririform plate invasion to subfrontal region underwent transfrontal excision, followed by radiotherapy treatment. Since 1979, the patient has remained free of tumor and asymptomatic. We believe that these tumors are slowly growing, and when presented at a late stage with intracranial extension, surgical resection, followed by radiotherapy and/or chemotherapy is an effective treatment.

SUPPORTIVE CARE DELIVERED IN THE HOMES OF END STAGE SARCOMA PATIENTS, S Volker, M Rice, JE Nyman, B Ortiz, R Wierzbicki, A Ezzat, King Faisal Specialist Hospital and Research Centre, Riyadh

Five patients with the diagnosis of end stage sarcomas were referred to the Home Health Care Program (HHCP) at King Faisal Specialist Hospital and Research Centre (KFSH&RC) for supportive care. Their mean age was 26 (16–44), with three females and two males. Three patients had bone sarcomas, and two soft tissue sarcoma. When referred to KFSH&RC, three had metastatic disease, one or two had local disease. All patients were treated in a multidisciplinary approach using surgery, chemotherapy, and/or radiation therapy. Patients were referred to the program with pain (5), wound infection (3), decreasing mobility (3), nutritional problems (2), and shortness of breath (1). Patients and their families were satisfied with this new service provided by KFSH&RC. The average time they stayed in the program was 6.5 weeks (range from 1–17 weeks). The objective and services provided by the program and the problems encountered will be presented.

TOXICITY OF ADJUVANT CHEMOTHERAPY WITH DOXORUBICIN/CDDP (AP) IN OSTEOGENIC SARCOMAS (OS), AA El-Warith, R Wierzbicki, A Ezzat, SM Kadhi, PG Moreau, R Asirvatham, J Antonius, K Sackey, T Khuwaitir, C Hugosson, King Faisal Specialist Hospital and Research Centre, Riyadh

A retrospective review of the medical records of 16 patients with osteogenic sarcoma (OS) presenting to King Faisal Specialist Hospital and Research Centre (KFSH&RC) from January 1989 to May 1991 was performed to analyze acute and short-term toxicity of adjuvant chemotherapy with AP. The median age was 15 years (range; 6–35 years). Male/female = 1/1. Patients received six courses of doxorubicin 25 mg/m(2)d × 3d + CDPP 100 mg/m(2) 24th IV infusion with pre and post hydration. For toxicity grading, the WHO criteria were used with the exception of electrolyte disturbances, where NCI(C) criteria were applied. Febrile neutropenia (FN) was observed in 12 (75%) of the patients. (Median number of FN episodes/patient is one, range 1–3). Grades 3 and 4 neutropenia, granulocytopenia, anemia developed in 13 (81%), 12 (75%), and seven (44%) patients, respectively. Thrombocytopenia Grade 3 was observed in only three patients. No cardiac or major neurotoxicity. Variable degrees of electrolyte disturbances developed in this group of patients, hypomagnesemia in 13 (81%), [with six (38%) Grades 3 and 4] hypokalemia in eight (50%) and hypocalcemia in eight (50%) patients. Altered renal functions as evidenced by a decrease of creatinine clearance (cr cl) was observed in three (18%) patients, (between 1.2–1 ml/Sec) which was reversible in all of them. Another patient had a drop of cr cl to 0.4 ml/sec in the postoperative period with elevation of S. creatinine and blood urea levels. (Renal biopsy showed auto immune glomerulonephritis). CDDP was omitted in the postoperative chemotherapy courses for these patients. Ten patients had dose modifications due to neutropenia. There were sixteen unscheduled admissions for febrile neutropenia, electrolyte disturbances, or both were needed. No toxic deaths were encountered. In conclusion, the major toxicities of adjuvant A/P were myelotoxicity and hypomagnesemia. Major nephrotoxicity secondary to CDDP was not seen. Follow-up of this group of patients for long-term chemotherapy toxicity is needed.

CHEMOTHERAPY FOR METASTATIC SOFT TISSUE SARCOMA IN ADULTS, R Wierzbicki, King Faisal Specialist Hospital and Research Centre, Riyadh

The soft tissue sarcomas represent a heterogenous group of neoplasms whose only common denominator is a derivation from mesenchymal tissue. Systemic chemotherapy for patients with metastatic disease remains of palliative intent. Doxorubicin (adriamycin) is the single most effective drug for the management of patients with metastatic soft tissue sarcoma, with response rates varying from 15–37%. There appears to be a steep dose response curve with response rates of 16% when doses of adriamycin 45 mg/m^2 were utilized, increasing to 28% when doses of 75 mg/m^2 were utilized. Recently, the alkylating agent ifosfamide has been found to be active in this disease, with, in untreated patients, a response rate of 25%. In the mid 1970s, SWOG explored the addition of other agents to adriamycin in a logical sequence of studies. The CYVADIC regimen showed in large numbers of patients a response rate ranging between 40–52% with 12–14% complete responses. Many investigators started to question the contribution of cyclophosphamide and vincristine and there was a move back to adriamycin with or without DTIC combinations. In the mid 1980s, the second generation of combination chemotherapy trials were developed by the addition of ifosfamide to adriamycin. NCIC(C) trial showed a response rate of 25% with adriamycin, dacarbazine and ifosfamide combination. The Dana Farber "MAID" protocol first described by Elias combines the same three agents in a different schedule. Their report of 47% response rate with this regimen has led to randomized trial in the United States in which MAID is compared to adriamycin and dacarbazine. The EORTC Sarcoma Group recently completed a randomized trial of adriamycin versus adriamycin + ifosfamide versus CYVADIC in untreated patients with soft tissue sarcoma with response rates of 25%, 25%, and 27%, respectively. Details of the above and other studies will be presented and discussion of future strategies to overcome drug resistence such as: identification of new active agents, improvement of therapeutic index by analogues, and dose intensification.

MULTI-MODALITY THERAPY FOR THE MANAGEMENT OF LOCALIZED EWING'S SARCOMA: ROLE OF SYSTEMIC CHEMOTHERAPY, R Wierzbicki, King Faisal Specialist Hospital and Research Centre, Riyadh

Surgery and radiotherapy were the main stays of therapy for Ewing's sarcoma (ES) prior to the 1960s. Local control was adequate, but failure-free survival with radiotherapy alone was only 9%. In 1971, a large trial of chemotherapy was begun by the Inter-Group Ewing's Sarcoma Study Group (IESS). In this study, patients were randomized to receive VAC (Vincristine, Dactinomycin, and Cyclosphosphamide), VAC with prophylactic whole lung irradiation, or VACA (VAC with addition of Adriamycin). At 24 months, the failure free survival was 74% with VACA, 58% with VAC plus irradiation, and 35% with VAC. A recent long-term follow-up of the first intergroup study continues to show superiority of VACA at five-year relapse free of 60% versus VAC—respectively 24% and VAC + radiotherapy 44%. Patients with disease at pelvic sites had significantly poorer survival at five years than those with disease at non-pelvic sites (34% versus 57%). The second inter-group study began in 1978 utilizing the best arm of IESS-1 and compared to treatment results obtained with relatively high dose doxorubicin and high dose cyclophosphamide. At median follow-up of 5.6 years, the overall outcome was significantly better on high dose intermittent method versus moderate dose continuing method. For non-pelvic primaries, five year disease free and overall survival was respectively 68% and 78% for high dose, versus 48% and 63% for moderate continuous dose. The survival of patients with pelvic primary tumors has improved as compared to historical controls of IESS-1 with 55% five year disease free survival versus 23%, and 63% overall survival versus 35%, respectively. Recently, two agents: ifosamide and etoposide, have demonstrated single agent activity in Ewing's Sarcoma. The single agent response rate for ifosfamide ranges from 0–45% and is approximately 30% for etoposide. There is currently an active Phase III inter-group study comparing the activity of vincristine, adriamycin, cyclophosphamide and dactinomycin with or without the addition of ifosfamide and etoposide in patients with newly diagnosed Ewing's sarcoma and peripheral neuro-epithelioma of bone. Attempts at dose intensification either by the addition of growth factors or autologous transplantation will be discussed.

OSTEOGENIC SARCOMA (OS) IN PATIENTS OVER 40 YEARS OF AGE, R Wierzbicki, A Ezzat, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, S El-Akkad, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and July 1991, a total of 148 patients with osteogenic sarcoma (OS) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). Median age of the whole group was 15 years. Eleven patients—8% were 40 years and older. Median age of that group was 47 years (range 40-80). Important differences between the group of older patients described here, and younger patients were identified as follows: ratio of male/female was 10–1 as compared to 1.3–1, 50% of patients presented with distant metastases as compared to 20% in the younger group, 25% of older patients had primary located within the bones of the knee joint, as compared to 70% in the younger group. One patient had post radiation OS. Chemotherapy (CT) consisting of adriamycin and platinum was given with palliative intent to four patients with metastatic disease—none responded. The median survival time of this small group of patients was eight months, overall survival 20% which is similar to 9 months and 20%, respectively in the below 40 age group. Out of six patients with localized disease, only one patient was offered adjuvant CT. This patient had no evidence of disease at ten month follow-up. In summary, there are important differences in characteristics of patients with OS in the older group bearing poorly on survival such as: high proportion of patients presenting with metastatic disease, lack of response to palliative CT, but also identified reluctance of physicians to suggest adjuvant CT.

OSTEOGENIC SARCOMA (OS) PATIENTS AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) 1980-1991,

R Wierzbicki, A Ezzat, A Bedikian, AA El-Warith, K Sackey, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, S El-Akkad, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and July 1991, a total of 148 patients with osteogenic sarcoma (OS) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). Median age was 15 years (range 6–84), M/F = 1.3/1, location of primary 102/148 (70%) were located around the knee joint (distal femur 69, proximal tibia 27, proximal fibula 6). In 114 patients, surgical staging was available–only five (4.3%) had Stages I-IIA, 95.7% had stage IIB and higher. Of 118/148 patients–80% presented without evidence of distant metastases, 30/148 with metastases–24 with isolated lung, six with multiple, 24/75 (30%) presented with metastatic disease prior to 1989, while 6/43 (14%) 1989–1991. In 95% of patients, presenting symptoms were swelling and pain, 90% had histologically classic OS. Mean numbers of patients referred per year were 14, and this had not changed appreciably since 1982. Fourteen out of 75 patients (19%) with localized disease seen prior to 1989 refused all treatments. Thirteen patients had surgery only (10 amputations, three limb salvage surgery), 15 patients (20%) had neoadjuvant chemotherapy (CT) followed by surgery, 33 patients had surgery followed by CT (21 amputations, 12 limb salvage). Out of 37 patients with localized disease referred between 1989–1991, 32 (86%) had neoadjuvant CT, while five (14%) had surgery followed by chemotherapy. MST (for 60 patients where information for survival was available) referred from 1980–1988 was nine months, with possible best overall survival (patients over three years NED even if lost follow-up)–21%. At 18 months, median follow-up of patients referred from 1989–40% are NED. Median DFS–nine months, MST–12 months. In summary, survival times given prior to 1989 can only be approximated. As compared to the period 1980–1988, the proportion of patients with metastatic disease referred from 1989 has decreased, the proportion of patients lost to follow-up, or refusing treatment has decreased considerably from 1989, and with all of the limitations of evaluation–the median survival and the overall survival appeared to be increased. Reasons for a relatively poor overall survival of patients from 1989 adequately treated with neoadjuvant CT are: - late presentations - stage 2 "B+", and compromise of dose intensity due to dose reductions secondary to 75% of patients having infectious episodes with neutropenia. Toxicity of CT is presented separately. In addition to treatment differences the results underline the foremost importance of communication between referring physicians so that early referral can be achieved as well as communications with patients since all patients from 1989 were informed about the diagnosis, treatment, and prognosis, perhaps this way improving the compliance and reducing the lost to follow-up, and refusal of treatments.

TREATMENT OF METASTATIC OSTEOGENIC SARCOMA (OS): KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) EXPERIENCE 1980-1991,

R Wierzbicki, A Ezzat, A Bedikian, AA El-Warith, K Sackey, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1990 and July 1991 a total of 148 patients with osteogenic sarcoma (OS) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). One hundred eighteen patients (80%) presented without evidence of distant metastases, 30 (20%) with metastases–24 with isolated lung, and six with multiple organ metastases. Demographic data and treatment results for those patients are analyzed. Median age 17 (range 10–74), M/F–1/1. Five patients were not offered, or refused chemotherapy. Twelve out of the remaining 25 patients (50%) were treated with adriamycin-platinum (AP) combination chemotherapy, while the remaining 13 patients with different chemotherapy regimens: Adriamycin +/– Vinca-alkaloid, +/– alkylating agents, high dose methotrexate, ifosfamide. Responses: 3/25–12% had PR, no CRs 22/25–88% had PD. All three responding patients were treated with adriamycin 25 mg/m^2 × 3 days plus platinum 100 mg/m^2 (day 1), with delivered relative dose intensity (DI) = 0.9. Median number of courses of AP given–two (range 1–7). Toxicity: nausea and vomiting grade 3 was universal. There was a 50% incidence of infectious episodes with neutropenia and no toxic deaths. There was Grade 3 hematological toxicity in 75% patients. Response rate for patients treated with AP - 3/12 = 25%. Median duration of response–two months. The remaining nine patients treated with AJP who did not respond had relative DI of both drugs 0.6. Second line chemotherapy was given in six patients consisting mainly of methotrexate and ifosfamide–no responses seen. There were no responses seen in patients with multiple organ metastases. Median survival time of 22 available for survival patients–seven months (range 2–36). In summary, results of palliative treatment of metastatic osteogenic sarcoma are unsatisfactory: 12% overall RR in all patients (25% PR with no CR in patients treated with AP regimen). There were no responses seen in patients treated without platinum. Therefore, our current policy is to offer investigational Phase II Studies for patients presenting with metastatic disease or recurrence after adjuvant AP and since July 1991, six patients were treated as part of a Phase II Study with second line chronic oral daily administration of VP–16 50 mg/m^2 × 21 days–no responses seen.

METASTATIC SOFT TISSUE SARCOMA: KING FAISAL SPECIALIST HOSPITAL EXPERIENCE,

R Wierzbicki, A Ezzat, F Khalifa, A Bedikian, AA El-Warith, R Sabbah, K Sackey, H Schultz, S El-Akkad, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, T Amin, M Abdulkareem, C Hugosson, J Antonius, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and 1991, a total of 107 patients with the diagnosis of metastatic soft tissue sarcoma (STS) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). These represented 21% of all STS referred to this hospital during this period. The median age was 29 years (range 4 days to 80 years), male to female ratio 1.2:1. Histologically, 15% had rhabdomyosarcoma, 14% malignant fibrous histiocytoma (MFS), 12% leiomyosarcoma, 12% spindle cell sarcoma, 10% STS unclassified, 6.5% fibrosarcoma, 6.5% clear cell sarcoma, and 24% other histology. Tumor was graded in only 32 cases, five (15.6%) Grade I, eight (26.6%) Grade II, and 19 (59.4%) Grade III. The most common site of metastases was the lung, 58% (31.8% confined to the lung and 26.2% lung and other sites). Lymph node metastases occurred in 26%, (histologically 21.4% had rhabdomyosarcoma, 10.7% synovial cell sarcoma, 14.3% STS unclassified, 7.1% MFH, 7.1% liposarcoma, 7.1% spindle cell sarcoma, 7.1% clear cell sarcoma and 25.2% other histology). Other sites of metastases were the liver 18%, bone 16%, brain 8%, bone marrow 2%, skin 2%, and small bone 2%. Sixty-seven patients were treated with chemotherapy (vincristine, cyclophosphamide, +/– actinomycin-D, +/– adriamycin). Eleven out of 67 patients with a histology of embryonal rhabdomyosarcoma had a remission rate of 81.8% with 36.4% complete remission (CR), 45.5% partial remission (PR), and median disease free survival (DFS) of 10.5 months [range 6–89 months]. The remaining 56 patients with other histology had a remission rate of 48%; 12.5% CR and 35.7% PR, with median DFS of patients in CR (7) = 60 months (range 5–85 months). For both groups, the two and five year overall survival rate was 16.4% and 6%, respectively.

SARCOMA WORKING GROUP (SWG) KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC): BACKGROUND AND ACTIVITIES,

R Wierzbicki, A Ezzat, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, C Hugosson, M Abdulkareem, J Antonius, K Sackey, H Schultz, S El-Akkad, V Saleh, S Al-Sedairy, K Sheth, King Faisal Specialist Hospital and Research Centre, Riyadh

Sarcomas are a heterogeneous group of malignant diseases requiring a combined effort of diagnostic and therapeutic modalities at various stages of patient disease. They are infrequent tumors so that any particular physician or institution rarely has an opportunity to see large numbers of patients and develop its own database and expertise. In February 1989, SWG was created with intended objectives: (a) for the development of a standardized workup and treatment plan, (b) for evaluation of results of previous and ongoing treatment, (c) used as an educational forum, (d) used as a forum for dissemination of clinical research information of current and projected protocols, (e) to serve as a liaison between pharmacy in the projected utilization of cytostatics. Membership involved representatives from the departments and sections of: General and Orthopedic Surgery, Pathology, Radiology, Research Centre, Oncology Nursing, Radiation Therapy, Pediatric Oncology and Medical Oncology. The first step was the development of standardized approaches to diagnosis, treatment and follow-up of soft tissue and bone sarcomas, which will be discussed in detail. In order to develop prospective demographic, epidemiological, and treatment data, a sarcoma survey and sarcoma database will be presented.

PATIENTS WITH LOCALIZED EWING'S SARCOMA (ES) AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) 1980–1991,

R Wierzbicki, R Sabbah, K Sackey, A Ezzat, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, S Kadhi, R Asirvatham, H Schultz, S El-Akkad, J Antonius, C Hugosson, P McArthur, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980–July 1991, a total of 135 patients with ES were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). Median age was 16 years (range 1–43), M/F-2/1, 91 (66%) of the patients presented without evidence of distant metastases, 44 (34%) with metastases of which 28 had pulmonary involvement and 16 with multiple organ involvement, including bone marrow. Location of primary: pelvis 26, ribs 22, femur 21, head and neck 12, humerus 12, fibula 10, vertebrae 10, tibia 6, scapula 5, foot 4, and extraosseous 4, clavicle 2, radius 1, 77/135, i.e., 58% of the patients with axial presentation, and 54/135 (42%) with extremity localization. Demographic data and treatment results will be analyzed for 91 non-metastatic patients. Forty-three out of 91 patients had a localized extremity primary of which 29/43 were treated with chemotherapy (CT) (cyclophosphamide, adriamycin, vincristine, +/– actinomycin-D; VP–16 + ifosfamide + platinum, followed by radiotherapy (RT), 10/43 were treated with CT followed by resection, and 4/27 (15%) of patients with localized extremity disease seen prior to 1989 refused all treatments. Forty-eight out of 91 patients (57%) presented with localized axial disease of which 27/48 were treated with CT followed by RT, 9/48 with CT alone, 3/48 with CT followed by surgery, 2/48 with surgery followed by CT, 3/48 with RT followed by CT, and 4/48 with RT alone. A median follow-up for all patients of 38 months, median survival time (MST) was 18 months, and three year disease free survival (DFS 22%). Eight percent (7/91) died from late relapses more than three years from diagnosis. MST for patients treated with CT followed by RT–18 months, three year DFS–14%. MST for patients treated with surgery after CT has not yet been reached, three year DFS 53% (median follow-up of 18 months for chemosurgical group versus 38 months for chemo/radiotherapy group). MST of patients with extremity versus axial localization was 18 months versus 19 months, respectively. From other prognostic factors in addition to tumor localization, tumor volume could not be evaluated, but LDH values were as follows: elevated LDH in 40% with localized ES (51% in axial versus 33% in extremity). MST for patients with elevated LDH = 14 months versus 18 months with normal LDH–NS. In summary, in an analysis of 91 patients with localized ES, there was no difference in survival between axial and extremity presentations or between patients with normal and elevated LDH.

LDH AS PROGNOSTIC FACTOR IN PATIENTS WITH EWING'S SARCOMA (ES): KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) EXPERIENCE,

R Wierzbicki, R Sabbah, K Sackey, A Ezzat, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, J Antonius, C Hugosson, P McArthur, King Faisal Specialist Hospital and Research Centre, Riyadh

LDH is reported to be an independent prognostic factor for response and survival for patients with Ewing's sarcoma (ES). From 1980–July 1991, a total of 135 patients with ES were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). Of those, LDH values are available for 88 patients. In 56/88 (65%), LDH was elevated. There were differences in localization with 75% and 46% elevation, respectively in axial versus extremity localization. There were also significant differences between patients with metastatic disease versus localized disease–respectively 80% and 55% of LDH elevation. In univariate analysis there was no significant difference in median survival times of patients with normal LDH versus elevated–respectively 18 and 14 months. There also was no difference in evaluation of long-term survivors–the proportion of patients with three years + DFS with LDH normal was 7/16 versus LDH elevated 9/16 (value of LDH was only available in 16 patients). Attempts at correlation between the value of LDH and survival and response to chemotherapy will be made, although this is hampered by KFSH&RC Lab changing the technique of measurement of LDH three times and therefore normal values. In conclusion, our data confirms the high proportion of patients with metastatic disease and axial presentation having elevated LDH but there appears to be no correlation in overall median survival times between patients with elevated LDH or normal.

LONG-TERM SURVIVAL OF PATIENTS WITH EWING'S SARCOMA (ES): KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) EXPERIENCE, R Wierzbicki, R Sabbah, K Sackey, A Ezzat, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, S El-Akkad, J Antonius, C Hugosson, P McArthur, King Faisal Specialist Hospital and Research Centre, Riyadh

Between 1980 and July 1991 a total of 135 patients with Ewing's sarcoma (ES) were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). The median survival of the whole group of non-metastatic patients (91/135 patients) was 18 months. In this abstract, demographic data and treatment results will be presented for a group of 20 patients alive NED more than three years. Median age 16 (range 5–35). Sex: M/F = 1/1.1. Nine out of 20 patients presented with extremity primaries, and 11/20 with axial presentation. In 45% of patients LDH was normal at presentation, 35% LDH elevated, and 20% unknown. Seventeen out of 20 patients (85%) were treated with chemotherapy (CT), (cyclophosphamide + adriamycin + vincristine + actinomycin–D) followed by radiotherapy (RT). Three out of 20 patients (15%) were treated with CT followed by surgery. Twenty out of 91 patients (22%) presented with localized Ewing's sarcoma are alive at three years without evidence of disease. (No patients presenting with metastatic disease survived beyond three years). In conclusion, the only difference in demographic characteristics of long-term survival versus all patients with localized Ewing's sarcoma was a higher proportion of females; otherwise, localization and LDH levels as well as treatment specifics were similar.

PATIENTS WITH METASTATIC EWING'S SARCOMA (ES) AT PRESENTATION: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) EXPERIENCE, R Wierzbicki, R Sabbah, K Sackey, A Ezzat, A Bedikian, AA El-Warith, RJ Rooney, PG Moreau, SM Kadhi, R Asirvatham, H Schultz, S El-Akkad, J Antonius, C Hugosson, P McArthur, King Faisal Specialist Hospital and Research Centre, Riyadh

From 1980-1991, a total of 135 patients with Ewing's sarcoma were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC). Of these, 44 patients (32%) presented with metastatic disease, demographic data and treatment results will be analyzed for this group of patients. Forty patients were given chemotherapy (CT) the remaining four were given palliative radiotherapy (RT) plus analgesics. Twenty four out of 40 patients (60%) presented with pulmonary metastases, and the remaining 40% with multiple organ metastases. CT regimen in 90% of patients was cyclophosphamide, adriamycin, and vincristine; in others, methotrexate, actinomycin–D, VP–16 ifosfamide were utilized. Results: overall response rate (PR + CR) was 65%, with median duration of response—three months. Response rate for patients with pulmonary metastases only—16/24 PR, 3/24 CR—total 19/24 = 80%. Response rate for patients with multiple organ metastases—5/16 PR + 1/16 CR = response rate 6/16—37%. Despite this difference in response rates there is no difference in median survival times between patients with pulmonary metastases only versus multiple organ—respectively ten months and nine months. There are no survivors beyond three years. In conclusions, systemic chemotherapy for patients presenting with metastatic disease is not curative and despite a significantly better response rate for patients with pulmonary metastases versus multiple organ metastases, there is no significant difference in median survival time between these two groups of patients.

A STUDY OF IMMUNOLOGICAL PARAMETERS IN SAUDI PATIENTS WITH OSTEOGENIC SARCOMA (OS), R Wierzbicki, S Al-Sedairy, AA El-Warith, R Parhar, A Ezzat, SM Kadhi, PG Moreau, R Asirvatham, J Antonius, H Schultz, C Hugosson, King Faisal Specialist Hospital and Research Centre, Riyadh

In an attempt to explore the immunological competence of Saudi patients with osteogenic sarcoma (OS) the following parameters were studied: (1) IL1 alpha, IL2, and IL6 levels (2) NK and LAK cell activity, (3) peripheral blood lymphocyte (PBL) proliferation in response to IL2 and PHA stimulation. Patient characteristics: 19 patients with localized OS presenting to King Faisal Specialist Hospital and Research Centre (KFSH&RC), from October 1989 to October 1991. Male/female – 11/8, median age 15.5 years (range 7–35 years). All patients were treated with pre- and postoperative chemotherapy with adriamycin + platinum + high dose methotrexate. Random samples were collected at presentation prior to surgery, postsurgery and after completion of chemotherapy. Results: the median levels of IL1, alpha (= 65.13 pg/ml) IL2 (= 3.4 μg/ml), IL6 (= 175 pg/ml) were uniformly elevated prior to, and after surgery. NK and LAK cell activity (median value 28, 37 at 100/l dilution, respectively) and PBL proliferation in response to IL2 and PHA (median level—11.5 and 11, respectively) were suppressed prior to surgery with a tendency of improvement of the latter after surgery (median -3.4 and -5.4, respectively). In conclusion, disturbed immunological functions in OS patients with elevated cytokine levels and depression of NK, LAK and T cell formation was observed. A trend for improvement of T cell function after surgery was also observed. A prospective longitudinal study is in progress.

PAIN CLINIC CONTRIBUTION IN PALLIATIVE CARE OF SARCOMA PATIENTS: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFSH&RC) EXPERIENCE, R Wierzbicki, AA El-Warith, A Ezzat, T Verghese, K Sami, G Lambert, PG Moreau, R Asirvatham, SM Kadhi, H Schultz, S El-Akkad, M Maghazil, KM Taibah, M Abuzeid, Z Mahasin, King Faisal Specialist Hospital and Research Centre, Riyadh

As a part of the comprehensive management of cancer and its complications, the Pain Clinic at King Faisal Specialist Hospital and Research Centre (KFSH&RC) is providing a pain control service. During the period of June 1989 to December 1991, 19 patients [M/F = 12/7] with sarcoma were referred to the Pain Clinic. The median age was 29 years (range 12–77 years). Thirteen had bone sarcoma (osteogenic sarcoma = seven, chondrosarcoma = four, ameloblastoma = 1 patient and six had soft tissue sarcoma (leiomyosarcoma = 3 and each of clear cell sarcoma, malignant schwannoma, spindle cell sarcoma and Ewing's sarcoma one patient. The location of the primary tumor was in the extremity = five patients, pelvis = three patients, chest wall = three patients, mandible = three, and five in other areas. This group of patients had a total of 88 Pain Clinic visits (median number of visits/patients = three, range 1–19). The main problem was secondary to: primary tumor in 11 patients (58%), metastases in six patients (21%), both in three patients (16%) and unrelated lumbar disc problems in one patient. Management of pain was primarily by analgesics (narcotics and co-analgesics). Epidural nerve block was done in one patient and partial cordotomy was done in another. Two patients refused invasive procedures for pain control. Good palliation was achieved in five (26%), incomplete relief of pain in seven (37%), no benefit in two (11%) and effect cannot be assessed in five patients who had single clinic visits. Utilizing Pain Clinic expertise will continue to provide optimum care for cancer patients.

MALIGNANT FIBROUS HISTIOCYTOMA OF BONE: A CLINICOPATHOLOGICAL STUDY, A Zaki, A Allam, N Moukhtar, A El-Goneimy, M Abou Ella, S Ezzat, National Cancer Institute, Cairo University, Cairo, Egypt

This study included an analysis of 19 cases of malignant fibrous histiocytoma (MFH) which presented to National Cancer Institute (NCI) during the period from January 1975 to December 1986. MFH constituted 17% of soft tissue sarcomas and 1% of bone tumors. The age of the patients ranged from 3–70 years with peak incidence between 24 and 40 years. The extremities were the most common site affected. The male to female ratio was 2.1:1. Four pathological types were identified being: spindle storiform (56%), myxoid type (24.5%), inflammatory type (12%) and giant cell type (2.5%). Regional lymph node involvement occurred in 10% of cases. The lung was the most common site of metastases (28%) followed by the bone (11%) and the liver (5%). Surgery was the main line of treatment in all cases followed by adjuvant postoperative irradiation. Chemotherapy was given in few cases and did not improve the prognosis survival. The local failure rate was 26% and the metastatic rate 32%. A five year actuarial survival rate amounted to 40%.

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

King Faisal Specialist Hospital and Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program, affiliated with King Saud University, the Royal College of Pathologists of Australasia and the Royal College of Pathologists of Great Britain.
3. Fellowships in the following areas. Cardiovascular Diseases: cardiology, pediatric cardiology, and thoracic and cardiovascular surgery. Oncology: hematology, medical oncology, and pediatric hematology-oncology. Medicine: endocrinology, gastroenterology, infectious diseases, nephrology, pulmonology and critical care, rheumatology. Pediatrics: allergy and clinical immunology, neonatal/perinatal medicine, gastroenterology and hepatology, infectious diseases, nephrology, neurology, and genetics, metabolic diseases, and endocrinology.

For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

Third International Course on Magnetic Resonance Imaging, Riyadh Armed Forces Hospital

The Third International Course on Magnetic Resonance Imaging will be held from 25 to 28 October 1992 (25 Rabi Al-Thani to 3 Jumada Al-Awal 1413). For further information, please contact: Riyadh Armed Forces Hospital, Department of Medical Studies, P.O. Box 7897, Riyadh 11459, Saudi Arabia. Tel.: (966) (01) 477-7714, extensions 2289/2269; Fax: (9661) 477-7194/477-9168.

King Faisal Specialist Hospital and Research Centre Academic Calendar for 1413H/1993G

King Faisal Specialist Hospital and Research Centre has scheduled the following Academic Calendar for 1992-1993G/1413H:

First Saudi AO Maxillofacial Course	15-18 Rabi Al Thani 1413 11-14 October 1992
Pan Pacific-Asian Conference III on Pharmacy Practice	22-24 Jumada Al-Awal 1413 16-18 November 1992
Symposium on Intervention in Acute Ischemic Syndromes	11-12 Jumada Al Thani 1413 5-6 December 1992
FMGEMS Examination	26-27 Rajab 1413 19-20 January 1993
Symposium on Nutritional Treatment and Intervention of Disease	4-5 Shaban 1413 26-27 January 1993
Symposium on Recent Advances in Diagnostic Radiology*	16-18 Shaban 1413 7-9 February 1993
USMLE Step 2	7-8 Shawwal 1413 30-31 March 1993
USMLE Step I	18-19 Dhu Al Hijjah 1413 8-9 June 1993

For additional information, please contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7238; Fax: (01) 442-7237.

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*Sponsored by the Joint Board for Postgraduate Medical Education.

The Fifth Asia and Ociania Congress of Nuclear Medicine and Biology

The Indonesian Society of Nuclear Medicine and Biology in cooperation with the National Atomic Energy Agency of the Republic of Indonesia shall act as the hosting body for the Fifth Asia and Ociania Congress of Nuclear Medicine and Biology to be held in Jakarta and Bali from 25 to 30 October 1992 (29 Rabi Al-Thani - 5 Jumada Al Awal 1413). For further information contact, Dr. Johan S. Masjhur, Chairman of the OC 5th AOCNMB, Department of Nuclear Medicine, School of Medicine Padjadjaran University, Dr. Hasan Sadikin Hospital, Jalan Pasirkaliki 192 Bandung 40161 Indonesia. Tel.: 62-22-85066; Fax.: 62-22-213937/62-22-612353/62-22-211282.

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The Directorate General of Health Affairs in the Eastern Province represented by Qatif Central Hospital is sponsoring a three day symposia on Pediatric Surgery in Saudi Arabia from 27 to 29 October 1992 (2-4 Jumada Al Awal 1413). In addition to speakers from Saudi Arabia and the Gulf Countries, distinquished speakers from abroad are invited.

Abstracts for presentation must be received no later than 30 August 1992 (20 Safar 1413).

For further information contact, Chairman, Scientific Committee, P.O. Box 18476, Qatif 31911, Saudi Arabia, Tel.: 8555000/ext. 2347 and 8540217/ext. 1024; Fax.: 8553691.

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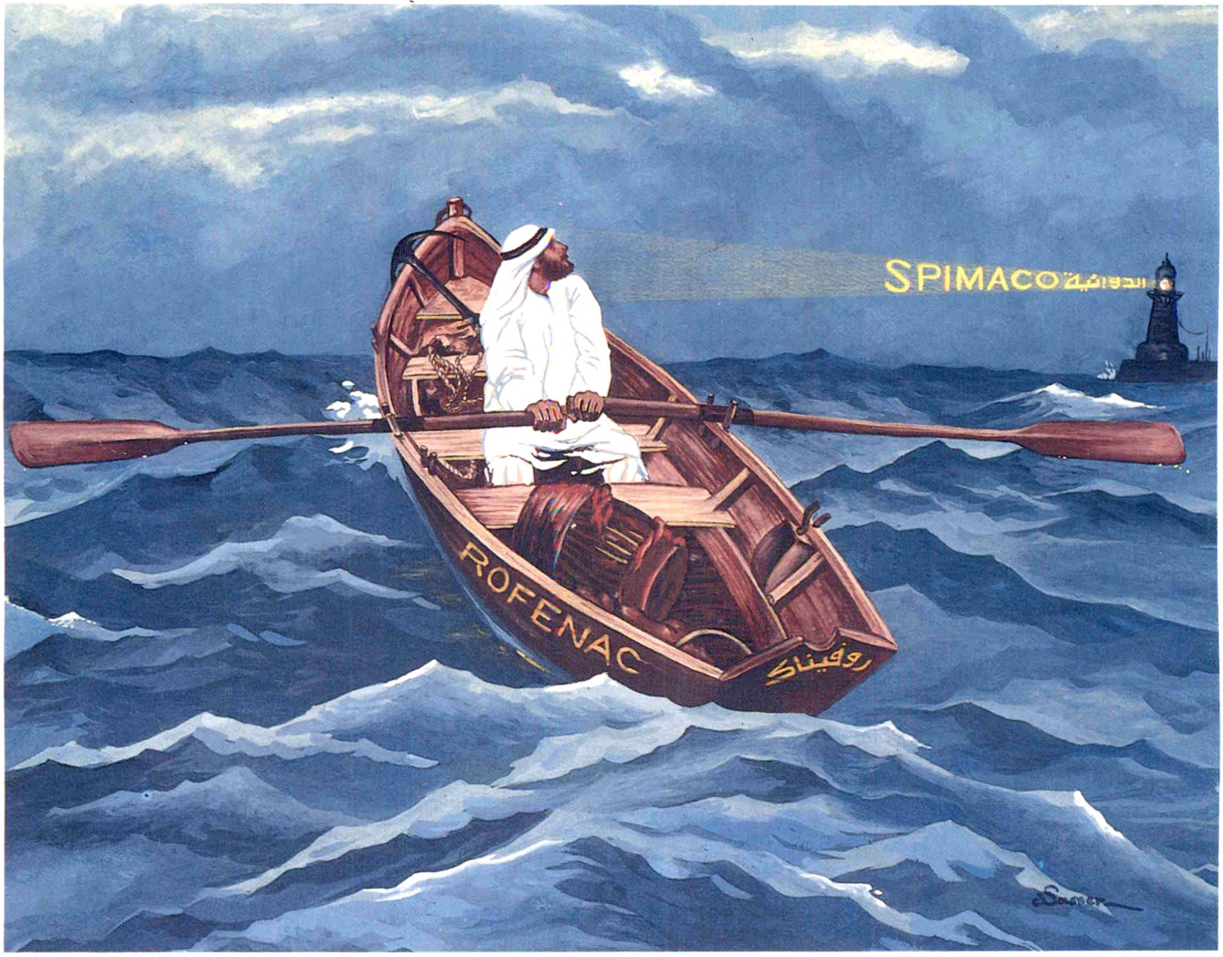

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The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."

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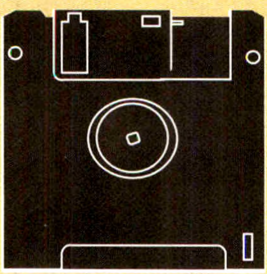

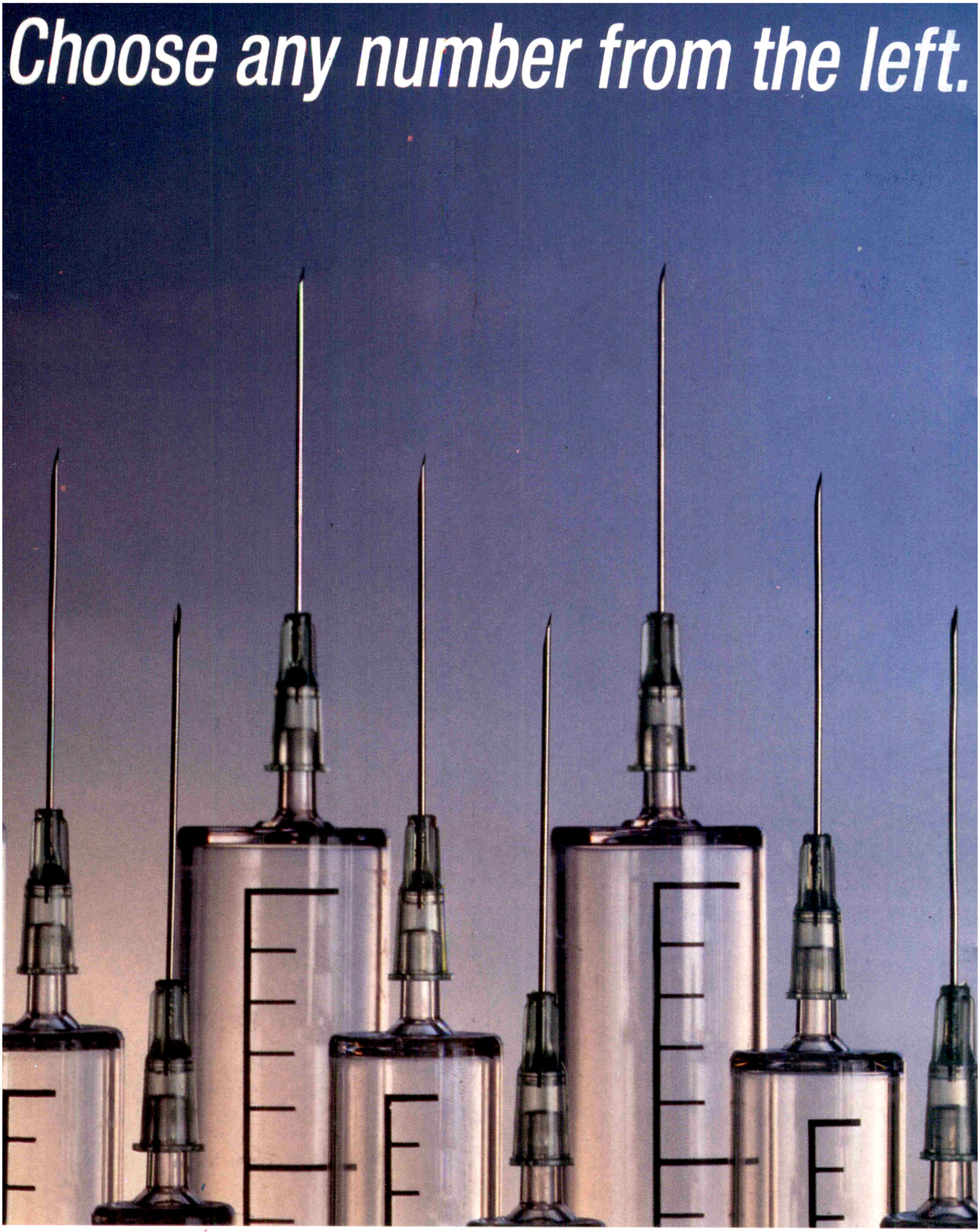

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INFORMATION FOR AUTHORS

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Editorial

BRUCELLOSIS: A MODEL FOR ERADICATION OF ENDEMIC DISEASES FROM THE ARABIAN PENINSULA

Wars, natural disasters, civil strifes, and famine come and go, but infectious diseases are going to stay with us forever. In this issue, there are 11 communications that focus on infectious diseases caused by parasites or bacteria. This underscores the persistence and the importance of parasitic and bacterial infectious diseases such as leishmaniasis, schistosomiasis, salmonellosis, and brucellosis in this part of the world. This also emphasizes the difference in the pattern of infectious diseases between developing and developed countries. The variation in the causation of infectious diseases makes the *Annals of Saudi Medicine* and the Saudi Medical Journal suitable for the presentation and discussion of infections that are pertinent to this part of the world. Medical journals elsewhere may regard these diseases as exotic or esoteric. One rarely sees a report on brucellosis in the American or European literature. In this issue, however, there are three communications that discuss the problem of brucellosis. This points out the fact that brucellosis remains a public health problem in the Arabian Peninsula. Certain infectious diseases have been eradicated on a wide scale with mass vaccination; others have been controlled by rigorous public health measures. The persistence of infections is due to the emergence of new mutants and the evolution of old diseases. Furthermore, the growth of the compromised host population due to the use of immunosuppressive agents or due to viral diseases such as AIDS has led to a change in the pattern of infectious diseases in Western countries.

The propagation of brucellosis, a zoonotic infectious disease, is predominantly due to the persistence of large reservoirs of the organism among livestock such as camels, sheep, goats, and cows.

Brucellosis is usually transmitted to man by drinking raw milk or consumption of its unpasteurized products such as cheese. Close contact with infected animals, milking of animals, handling infected animal meat or contact with placental membranes are other modes of transmission of brucellosis. The current reports from various regions, especially remote villages and Bedouin communities of Saudi Arabia, point to a serious health problem [1–3]. Visitors to endemic areas may become infected by consumption of infected animal products. Furthermore, with air travel, geographic barriers of diseases are being disrupted. The disease is both curable and preventable. In this issue, new fluoroquinolones have been found to be effective *in vitro* against isolates *Brucella melitensis* [4]. Several other antibiotics are also effective against the disease. Early detection and prompt treatment are mandatory.

The General Directorate of Infectious and Parasitic diseases (GDIP) at the Ministry of Health (MOH) in the Kingdom of Saudi Arabia has established programs for the training of laboratory technicians in the detection of brucella antibodies. In addition, health education programs for brucellosis have been initiated by the Ministry of Health in collaboration with the Ministry of Agriculture for personnel handling livestock and for the general public. Furthermore, a brucellosis control committee consisting of members from the Ministry of Health, Ministry of Agriculture, and the Ministry of Municipalities and Rural Affairs has been established. The major objective of this committee is the eradication of brucellosis from Saudi Arabia. The Ministry of Agriculture has been very active in this area and its efforts in the control of infection among livestock are very much appreciated. Camels, sheep, cows, and goats may cross the borders of countries of the Arabian Peninsula either by trade, by shepherds, or in the wild. Currently, there is no legislation governing the migration of livestock. It is possible that *Brucella* infected animals may cross the borders without any restrictions.

Prevention of brucellosis should be given top priority by the health authorities of the countries of the Arabian Peninsula. Wide scale mass livestock vaccination with attenuated strains of *Brucella* organism is safe and effective. All infected livestock should be exterminated. Public health education programs should be initiated. Joint efforts among the GCC countries should be encouraged to initiate collaboration on the prevention of brucellosis from the Arabian Peninsula. Health collaboration among the GCC countries could make brucellosis a model for the eradication of endemic diseases from the Arabian Peninsula.

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Original Articles

THE GROUP SPECIFIC POLYSACCHARIDE ANTIBODY IN CHILDREN WITH NON-SUPPURATIVE SEQUELAE OF GROUP A STREPTOCOCCAL INFECTION

Hasan A. Majeed, FRCPI, DCH; Abdul Mohsen Yousof, FRCP, PhD;
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تمت دراسة حركية الأضداد المناوعة لعديدة السكريد من الفئة (أ) لدى الأطفال المصابين بحمى رثوية حادة ولا يعانون من التهاب في القلب، وفي الأطفال المصابين بحمى رثوية حادة مع التهاب في القلب وأصيبوا لاحقًا بداء القلب الرثوي وفي الأطفـال المصـابين بالتهاب حاد في الكبب والكلية بسبب المكورات العقدية. تم علاج الأطفال المصابين بالحمى الرثوية وبالتهاب في القلب والذين لا يعانون من التهاب القلب بالعقاقير الواقية من المكورات العقدية بصفة مستمرة. كان عيار الأجسام المضادة في البداية في مجموعة الأطفال المصابين بداء القلب الرثوي مرتفعًا بصورة واضحة مقارنة بالذين يعانون من حمى رثوية ولكن بدون التهاب في القلب (الأحتمال P = ٠,٠١). وبعد فترة متابعة متوسطها ثلاث سنوات ظل العيار مرتفعًا فقط في الأطفال المصابين بداء القلب الرثوي، إذ كان مرتفعًا بصورة واضحة بمعدل أعلى من العيار الذي تبين في الأطفال المصابين بحمى رثوية ولكن بدون التهاب في القلب (الاحتمال P = ٠,٠٠١) وفي الأطفال المصابين بالتهاب الكبب والكلية بسبب المكورات العقدية (الاحتمال P = ٠,٠٠١).

The kinetics of the group A specific polysaccharide antibody were studied in children with acute rheumatic fever who had no carditis, children with acute rheumatic fever who had carditis and developed rheumatic heart disease and in children with acute poststreptococcal glomerulonephritis. The children with rheumatic fever who had carditis and those who did not, were kept on continuous antistreptococcal prophylaxis. In the group of children who developed rheumatic heart disease the titer of the antibody at onset was significantly higher than those who had rheumatic fever but no carditis ($P = 0.01$). After a mean follow-up period of three years, a high titer was maintained in children who developed rheumatic heart disease only and was significantly higher than that found in children with rheumatic fever who had no carditis ($P = 0.001$) and in children with poststreptococcal nephritis ($P = 0.001$).

The role of group A streptococci in the pathogenesis of acute rheumatic fever (ARF), seems to be beyond dispute [1]. Three mechanisms have been suggested, namely a direct toxic reaction of a streptococcal antigen, a persistant infection with streptococci or streptococcal variant organisms and an abnormal host immunologic response with immunologically mediated host tissue injury [2]. Evidence has been accumulating which has led to the consideration of the host immunologic response as being central to the development of ARF [2]. The possibility of a relationship between the immune response and the disease process gained important support from the pioneering work of Kaplan and Meyeserian who reported an immunological cross-reaction between the streptococcal cell wall and human heart tissue [3]. Since then, multiple cross-reactive systems have been reported between streptococcal antigens and human tissues. These included: cross-reactions between the streptococcal cell membrane and the human heart sarcolem-

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mal sheaths [4,5], streptococcal cell membrane and basal ganglia [6], streptococcal M protein and myosin [7], the hyaluronic acid of the streptococcal capsule and the human synovial tissue [8], and the group A specific polysaccharide and the glycopeptides of the heart valves [9,10]. The latter finding was strengthened by the work of other colleagues who reported that elevated levels of the group A specific polysaccharide antibody (CHO-Ab), in the presence of normal titers of antistreptolysin O (ASO) and anti $DNA_{se}B$, was only maintained in patients with ARF who developed rheumatic heart disease (RHD) [11–13]. Acute rheumatic fever, RHD and acute poststreptococcal glomerulonephritis (AGN) are still common in Arab countries [14–22]. However, to the best of our knowledge, no studies of the kinetics of the CHO-Ab have so far been reported from such countries. This may be the first study conducted in this part of the world.

Patients

The study population consisted of three groups. Group 1 included 15 children with the initial attack of acute rheumatic polyarthritis; Group 2 of 15 children with the initial attack of ARF where carditis progressed to RHD, and Group 3 included 13 children with AGN. All children were of Arab origin and followed-up from 3–3.8 years.

Groups 1 and 2 were maintained on monthly benzathine penicillin G; whereas Group 3 was placed on oral penicillin for ten days only. Children were investigated within 48 hours of admission to the hospital and on subsequent follow-up visits. All sera were separated and stored at –20°C until tested. Of the 15 children with ARF and RHD, 11 had mitral incompetence, and four had aortic and mitral incompetence. Table 1 shows the demographic data of the three groups of children. The diagnoses of ARF and AGN were based on internationally accepted criteria [23,24].

Methods

The C-polysaccharide (CHO) was extracted from the cell walls of group A streptococci with formamide as previously described [25].

Indirect micro-solid phase RIA [26] was carried out on disposable microtiter plates (COOKE, England/USA), using a sandwich technique. The fixation of the antigen was performed in the concentration of 0.5 μg/50 μl PBS buffer per well; (purified C-CHO was used in a concentration of 10 μg/ml PBS, pH 7.2, 15 μl were inserted into each well and kept overnight at 4°C, followed by washing three times with PBS). The sera were diluted in PBS buffer containing 1% bovine serum albumin. (200 μl of 1% bovine serum albumin in PBS were added to each well and kept overnight at 4°C followed by washing three times with PBS). Specific antibodies were detected by Protein A (PHARMACIA - Sweden) labeled with iodine 125 (AMERSHAM, England) (serum specimens 1:10 in PBS were diluted with 1% BSA in auxiliary tubes. 100 μl of PBS/BSA were added into the six wells of the microtiter plate; 25 μl of serum diluted 1:10 were transferred into the first well; after mixing, 25 μl were transferred to the next well and this was repeated until the sixth well, incubated overnight followed by washing three times with PBS. In using this method, serial dilutions with a quotient of 4/serum, 1:40, 1:160, 1:640, 1:2560, 1:10240 and 1:40960 were obtained. 50 μl of Protein A labeled with iodine 125 were added to each well in a concentration of 50 μg/ml PBS/BSA, and kept overnight at 4°C followed by washing three times with PBS). Dosimetry was carried out on Gamma Counter (Crystal II Multidetector, RIA System, Packard-Canberra, USA). Results were calculated from cpm values according to negative and positive standards of serum. The positivity was expressed in dilution titers. Each specimen was tested in fourfold dilution ranging from 40–40960. The titer of antibody was determined by interpolation; it was expressed by reciprocal value of serum dilution given by the point of intersection of titration curve with a line corresponding to the value of cpm of negative standard in the dilution 1:40. The negative standard was obtained from ten normal sera from Kuwait. The positive standard was obtained from known C–CHO antibody titers. The determination of ASO and DNAseB titers were carried out as described previously [27,28]. Statistical analysis of the differences in distribution was performed using the Mann-Whitney U-Rank Test.

Results

Table 1 shows the basic data of the three groups. Table 2 shows the log of the Geometric Mean Titer

(GMT) of the antibodies in the three groups at the onset and end of follow-up. Table 3 shows the statistical differences of antibody titers among the three groups at onset and end of follow-up.

Figure 1 shows the distribution of CHO-Ab titers in the three groups at onset and end of follow-up.

Discussion

Among the cross-reactive antibodies, CHO-Ab is of special interest because, in addition to cross-reactivity with the structural glycoproteins of the human cardiac valves [9,10], it has been reported to persist after an ARF attack only in patients who developed RHD [11–13]. The difference, however, could not be confirmed in a large series of patients studied with the agar diffusion precipitation technique [29] rather than the radioimmunoassay.

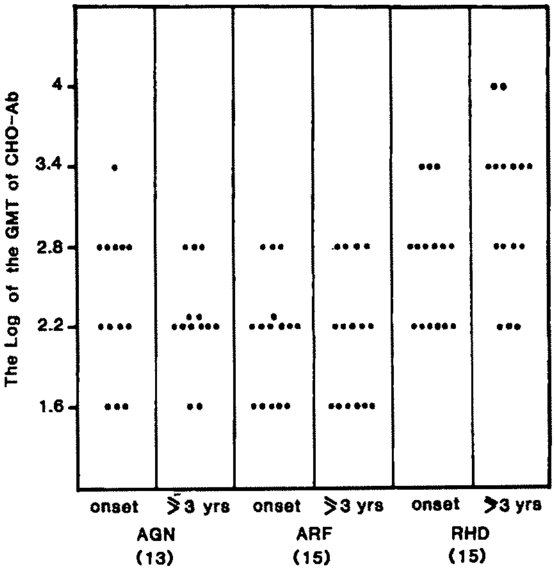

FIGURE 1. The distribution of carbohydrate antibody titers in the groups at onset and at end of follow-up.

At onset, the titer of the CHO-Ab in the RHD group, was significantly higher than that of the

TABLE 1. *Demographic data of the three study groups.*

		Age (years)		Sex		Follow-up (yrs)	
Diagnosis	No.	Range	Mean	Male	Female	Range	Mean
ARF	15	5–12	9	8	7	2.4–5.3	3.8
RHD	15	5–16	9.5	12	3	2.5–5.2	3.8
AGN	13	3–11	6.5	7	6	2–4.3	3

ARF = acute rheumatic fever; RHD = rheumatic heart disease; AGN = acute glomerulonephritis.

TABLE 2. *Logs of the geometric mean titers of the CHO-Ab at the onset and at the end of follow-up in the three groups.*

	CHO-Ab		ASOT		ANTI DNA$_{se}$B	
Group (No.)	Onset	FU	Onset	FU	Onset	FU
RHD (15)	2.69	2.96	2.53	2.38	2.7	2.38
ARF (15)	2.12	2.12	2.56	2.26	2.75	2.35
AGN (13)	2.39	2.25	2.66	2.57	2.75	2.67

FU = follow-up.

TABLE 3. *The statistical differences in the logs of the GMT of the three antibodies at onset and at follow-up.*

	P at onset			*P* at follow-up		
Group	CHO Ab	ASO	Anti DNA$_{se}$B	CHO Ab	ASO	Anti DNA$_{se}$B
RHD vs ARF	0.017*	0.66	0.8	0.001*	0.15	0.37
RHD vs AGN	0.22	0.208	0.67	0.001*	0.05*	0.14
ARF vs AGN	0.12	0.46	0.83	0.5	0.004*	0.06

* Statistically significant.

ARF group, but not that of the AGN group (Table 3). However, at the end of the follow-up period, the titer of the CHO-Ab in the RHD group was significantly higher than those of the ARF and AGN groups (Table 3). This is a relevant finding since both the RHD and ARF groups were maintained on continuous antistreptococcal prophylaxis, whereas the AGN group was not. This is clearly demonstrated by the findings that at the end of follow-up, there were no significant differences in the titers of the ASO and anti $DNA_{se}B$ between the ARF and RHD groups (Table 3), whereas the titers of these two antibodies were higher in the AGN group than both RHD and ARF groups; the differences were significant for the ASO-Ab ($P = 0.05$, $P = 0.004$) (Table 3). On the other hand, the finding that at the end of follow-up the three antibodies were higher in the AGN group than the ARF group can probably be explained by the fact that the AGN group then was not on secondary prophylaxis and streptococcal infections over the three-year period may have contributed to the rise of the titer of the three antibodies.

Data from this study show that the children in the three groups had elevated levels of CHO-Ab during the acute stage of the disease; however, the level remained elevated only in the group with valvar RHD. This confirms the report of Dudding and Ayoub [11]. These findings suggest that this subgroup of patients have an exaggerated immune response to the group A streptococcal antigen which has been shown to persist for prolonged periods of time in the host. It is probably worth stressing that this CHO antigen was also shown to share antigenic determinants with the valvar glycoprotein of heart tissue [10]. These findings are important for researchers; however they are also of diagnostic help in clinical practice. Patients with congenital heart disease or mitral valve prolapse were shown to have normal CHO-Ab levels [30]. Furthermore, in a situation where patients do not have a well documented attack of ARF and in whom one is unsure of whether mitral valve insufficiency is of rheumatic or non-rheumatic etiology, the findings of an elevated CHO-Ab level in the presence of normal ASO and anti-$DNA_{se}B$ titers favor a rheumatic etiology [30].

A possible disadvantage in our study may be the lack of normal controls. However, in a previous publication, we showed that the titers of the CHO-Ab were significantly higher in a group of children with ARF and another with RHD than those in children with non-complicated streptococcal pharyngitis in Kuwait [31]. Furthermore, the significant differences in the comparative dynamics of the three antibodies over a mean period of three years in the three groups are obvious.

In conclusion, data from this study confirm that in children with the non-suppurative sequelae of group A streptococcal infection, persistent elevation of the CHO-Ab occurred only in patients who developed RHD; this finding is of importance for both researchers and clinicians.

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أظهرت مراجعة للحالات التي أدخلت إلى أجنحة الأطفال في مستشفى الملك خالد الجامعي بالرياض بالمملكة العربية السعودية على مدى أربع سنوات (١٩٨٥ ـ ١٩٨٩م) أن الأمراض الرئيسية التي عانى منها الأطفال كانت المشكلات إبان الولادة والالتهابات التنفسية الحادة والشذوذات الولادية وأمراض الجهاز العصبي المركزي. وباستثناء ما لوحظ من الرخد الغذائي فقد كان سوء التغذية نادر الحدوث. أظهر توزيع الأعمار أن أغلبية الحالات كانت من الولدان والرضع الذين بلغت نسبتهم ٤٢,١٪ و٥٣,٦٪ على التوالي. كان هناك تفاوت موسمي، حيث كان عدد الأطفال الذين ادخلوا المستشفى خلال أشهر البرد من السنة (من نوفمبر إلى أبريل) أكبر من عددهم في أشهر الحر (من مايو إلى أكتوبر). وقد تبين أن الالتهابات التنفسية الحادة كانت في الأغلب سبب هذا التفاوت. وقد ظهرت العوامل الوراثية والعائلية بشكل واضح كأسباب لكثير من الاضطرابات التي أدخل من أجلها الأطفال إلى المستشفى. لذا نوصي بإيلاء اهتمام متزايد لطب الولدان والوراثة والإرشاد الوراثي لكونها عناصر هامة في الممارسة الطبية في المملكة. ومن الأمور المرغوب فيها كذلك إنشاء معهد وطني يختص بعلم الوراثة البشرية.

A review of admissions into the pediatric wards of the King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, over a four-year period (1985–1989) identified perinatal problems, acute respiratory infections, congenital anomalies and diseases of the central nervous system, as the major disorders. With the notable exception of nutritional rickets, malnutrition was rare. The age distribution showed a preponderance of neonates and infants who represented 42.1% and 53.6% of all admissions, respectively. There was a seasonal variation with more patients being admitted during the cool months of November-April than the hot months of May-October, and acute respiratory infections were found to be mostly responsible for this seasonality. Genetic and heredofamilial factors featured prominently in the pathogenesis of many of the disorders for which the children were admitted. It is therefore recommended that increased attention be given to neonatology and to genetics and genetic counselling as important components of medical practice in the country. The establishment of a National Institute for Human Genetics is also highly desirable.

Health services, including Child Health Services, have expanded dramatically in the Kingdom of Saudi Arabia during the past two decades [1,2], but there is, as yet, very little information in the medical literature about the pattern of diseases among Saudi children. Estimates of health situations in the community are best provided by a comprehensive health information system, but routine collection of vital statistics and other health data are currently unavailable in Saudi Arabia [3]. In such circumstances, it has been recommended by the World Health Organization (WHO) and other authorities [4,5], that hospital-based data could be used to provide estimates of health status in a community and for planning purposes.

The King Khalid University Hospital (KKUH) was opened in April 1982 as the main teaching hospital of the King Saud University (KSU). It has a capacity for 800 beds including 91 admission

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facilities for children, consisting of 68 beds and cots for general and speciality cases, and 23 incubators and cots for newborn infants. In addition to serving as a tertiary referral and teaching center, KKUH also operates an active primary health care service with 24-hour emergency coverage.

The present analysis of pediatric admissions in KKUH is undertaken to determine: (1) the common diseases for which children are admitted into the hospital; (2) the sex and age characteristics of the patient; and (3) the monthly and seasonal distribution of admissions.

Material and Methods

Diagnostic coding of all admissions using the ninth revision of the International Classification of Diseases (ICD) [6] has been in operation at KKUH since its inception. The coded diagnoses and other relevant data for each patient are stored in the King Saud University mainframe computer through a terminal at KKUH. For the purpose of the present study, the stored data for the period April 1982 to August 1989 were retrieved from the computer storage system and analyzed. In patients with multiple diagnoses, only one diagnosis (the primary or main diagnosis) was recorded for each patient. Similarly, if a patient had more than one admission during the period covered by the study, only the first admission was selected for analysis. Each patient was therefore represented only once in the study. Whenever clarification of any information about a patient was found necessary, the case file of the patient was retrieved and reviewed.

Results

Preliminary evaluation of the retrieved data revealed considerable gaps in the entries made between April 1982 and August 1985. The present report is therefore restricted to the admissions from 1 September 1985 to 31 August 1989, during which period reliable data were available. A total of 26,525 patients had admissions into the hospital wards during the above stated period. A total of 11,900 (44.9%) were children aged 0–12 years, and constituted the subjects of the present analysis. There were 7,323 males and 4,577 females, giving a male to female ratio of 1.6:1. The largest age group among the admissions were infants (0–1 year) who constituted 53.6% of the total (Figure 1). Neonates (0–1 month) numbered 5,057 and constituted 42.5% of the total. Seventy one percent of the children were aged less than two years while only 9.2% were aged more than five years. Males outnumbered females in all the age groups (Figure 1). The major diagnostic categories are presented in Table 1.

TABLE 1. *Diagnostic categories among 11,900 pediatric admissions into KKUH, Riyadh, 1985–1989.*

	Year				
Major diseases (ICD–9)*	1985/86	1986/87	1987/88	1988/89	Total (%)
Diseases of the neonatal period (760–779)	852	1205	1468	1483	5008 (42.1)
Congenital anomalies (740–759)	305	516	618	478	1917 (16.1)
Respiratory disorders (460–519)	338	559	627	337	1861 (15.6)
Diseases of the nervous system (319–382)	154	247	273	192	866 (7.3)
Enteritis and colitis (555–569)	121	135	128	79	463 (3.9)
Hematological diseases (280–289)	72	123	127	121	443 (3.7)
Acute GIT and abdominal surgical disorders (550–554)	74	130	143	42	389 (3.3)
Endocrine, nutritional and metabolic disorders (240–279)	67	79	63	69	278 (2.3)
Infectious and parastic diseases (001–139)	32	41	34	109	216 (1.8)
Genitourinary diseases (580–629)	28	41	52	45	166 (1.4)
Miscellaneous	73	108	59	53	293 (2.5)
Total	2116	3184	3592	3008	11,900 (100.0)

* ICD coding in parenthesis.

Neonatal Disorders (Excluding Congenital Anomalies)

These were responsible for 5,008 admissions. The most common disorder was neonatal jaundice which affected a total of 2,480 neonates admitted during the study period. Identified etiological factors of neonatal jaundice included ABO incompatibility (14.5%), Rh incompatibility (12.4%), prematurity (11.2%), neonatal sepsis (5.6%), and G6PD deficiency (0.8%). In more than 50% of cases, no causative factor of jaundice was documented. The unconjugated bilirubin levels were in the phototherapy range in most cases, and only rarely was exchange blood transfusion (EBT) required. The diagnoses in the other admitted neonates are listed in Table 2.

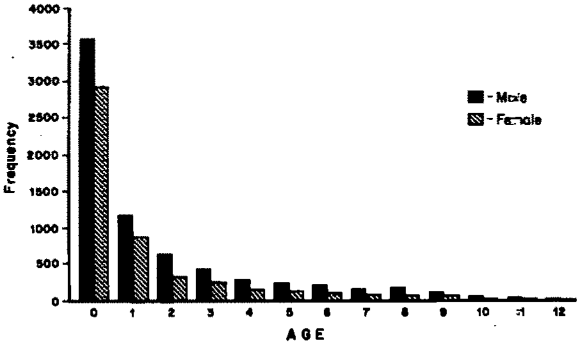

FIGURE 1. Sex and distribution of pediatric admissions at KKUH, Riyadh, Saudi Arabia (1985–1989).

TABLE 2. *Diagnoses among 5,008 neonates admitted into KKUH, Riyadh, 1985–1989.*

Neonatal disorders	No. affected (%)*
Perinatal jaundice	2480 (49.5)
Prematurity/intrauterine growth retardation	467 (9.3)
Birth asphyxia	278 (5.6)
Maternal complications of pregnancy	261 (5.2)
Postmaturity and high birth weight disorder	192 (3.8)
Endocrine + metabolic disorders	169 (3.4)
Temperative regulative disorders (mainly hyperthermia)	154 (3.1)
Infections (neonatal sepsis)	151 (3.0)
Maternal illness	141 (2.8)
Birth trauma	109 (2.2)
Hemorrhagic disease of the newborn	106 (2.1)
Others	500 (10.0)
Total	5008 (100.0)

* % of total.

Congenital and Chromosomal Disorders

These are listed in Table 3. Multisystem abnormalities were common in 117 cases, major abnormalities occurred in more than one organ system. The 114 chromosomal syndromes verified were: Down syndrome (68 cases), Klinefelter syndrome (27 cases), Edward (9 cases), Turner (8 cases) and Patau (2 cases).

Respiratory Disorders

The three main diagnostic categories among the 1,861 children admitted for respiratory disorders were acute upper respiratory tract infections (pharyngitis, laryngotracheitis), lower respiratory tract infections (bronchiolitis, bronchitis, bronchopneumonia, and lobar pneumonia), and asthma which were the diagnoses in 976,520 and 318 patients, respectively.

Examination of the monthly distribution of the respiratory admissions revealed that 1,283 patients were admitted during the cool months of November to April compared with 578 admitted during the hot months of May to October. This seasonal variation is statistically significant ($Z = 13.89, P < 0.001$).

Diseases of the Nervous System

Seizure disorders (epilepsies), static encephalopathies (cerebral palsy) and mental retardation were the three leading neurological diagnoses (Table 4). Not infrequently, two or all three of these chronic neurologic disorders coexisted in the same child but as already explained, each patient was assigned only one (primary)

TABLE 3. *Principal diagnosis among 1,817 children with congenital anomalies in KKUH, Riyadh, 1985–1989.*

Congenital anomalies	No. of children (%)*
Musculoskeletal anomalies	497 (25.9)
Genitourinary anomalies	329 (17.4)
Central nervous system anomalies	203 (15.8)
Gastrointestinal (including cleft lip and palate)	289 (15.1)
Cardiovascular system anomalies	227 (11.8)
Respiratory system anomalies	41 (2.1)
Multiple systems	117 (6.1)
Chromosomal syndromes	114 (5.9)
Total	1817 (100.0)

* % of total.

TABLE 4. *Diagnoses among 866 admissions with disorders of the nervous system in KKUH, Riyadh, 1985–1989.*

Nervous system disorders	No. of children (%)*
Seizure disorders	216 (24.9)
Static encephalopathies	178 (20.6)
Psychomotor (mental) retardation	164 (18.9)
Heredodegenerative disorders	77 (8.9)
Febrile convulsions	62 (7.2)
Bacterial meningitis	49 (5.7)
Muscular dystrophies	34 (3.9)
Peripheral neuropathies	19 (2.2)
Others (miscellaneous)	67 (7.7)
Total	866 (100.0)

* % of total.

diagnosis. The spectrum of diagnoses in the 77 children with heredodegenerative disorders of the central nervous system has recently been reported by Mahdi [7]. Noteworthy among the miscellaneous neurological disorders was subacute sclerosing panencephalitis (SSPE) which was diagnosed in 14 children; these were recently reported by Mahdi and Familusi [8].

Disorders of the Gastrointestinal Tract

Gastroenteritis was diagnosed in 463 children. A majority of these were probably of viral origin because bacterial agents were isolated from the stools in only a few of the cases. Various acute surgical disorders of the GIT were the diagnoses in 389 other children.

Diseases of Blood and Blood Forming Organs

The most common hematological disorders were the sickle cell hemoglobinopathies and the thalassemias which were diagnosed in 207 children, most of whom had multiple admissions because of crises, and for elective blood transfusions as part of their routine management. Iron deficiency anemias were diagnosed in 82 children while the purpuras, particularly Henoch-Schonlein purpura, and in 46 others, idiopathic thrombocytopenia purpura was diagnosed. Fifty-two children had leukemias or lymphomas; most of the affected children also had multiple admissions for management of relapses, but as already indicated, each patient was counted only once.

Endocrine, Metabolic and Nutritional Disorders

The most common diagnosis in this group was rickets which affected 61 children. Protein calorie malnutrition was relatively rare with only one admission for Kwashiorkor and 16 admissions for nutritional marasmus.

Infections and Parasitic Diseases

These were responsible for only 216 admissions (Table 1). Notable in this group were various bacterial and protozoal infections (42 cases); viral and chlamydial infections (41 cases); and candidiasis (38 cases). Tuberculosis and measles accounted for only nine and three admissions, respectively. There were no admissions for acute paralytic poliomyelitis, but 22 children were admitted for orthopedic management of the late effects of paralytic poliomyelitis. Congenital syphilis was diagnosed in four cases. Malaria was diagnosed in nine children, all of whom had recently arrived in Riyadh from abroad, or from areas of the Kingdom where malaria remains a health hazard.

Genitourinary Tract Disorders

The most common diagnosis in this group was nephrotic syndrome which affected 76 or 45.8% of the 166 children admitted for genitourinary disorders. The next most common diagnosis was chronic renal failure in 35 children most of whom were on chronic peritoneal dialysis programs pending renal transplantation. As has been previously noted by Abdurrahman and Elidrissy [9], heredofamilial factors were often involved in the pathogenesis of the genitourinary disorders.

Miscellaneous Disorders

Noteworthy among the miscellaneous diagnoses were subcutaneous cellulitis and abscesses diagnosed in 78 children, atopic dermatitis diagnosed in 33 children, and severe urticaria in 25 others. Thirty-four children were admitted for accidental ingestion, usually of drugs prescribed for their parents. Road traffic accidents did not feature prominently in the present analysis because affected children were rarely admitted into pediatric wards.

Monthly Distribution and Seasonality of Admissions

Admissions were consistently higher during the cool months of November to April than during the hot months of May to October, and as already noted, one major contributor to this seasonality are acute respiratory infections which occurred more frequently during the cool months.

Discussion

Hospital-based data are selective and at best, reflect only the general pattern of diseases in a given population. They are nevertheless of value, particularly in countries where vital statistics and other sources of health information are lacking.

The preponderance of infants, and in particular neonates, among the admissions in the present series is noteworthy. Infants constitute 53.6% of all the pediatric admissions and 42.5% were neonates (less than one-month-old). This preponderance of neonates and infants among the hospital admissions probably reflects the high birth rate which is currently 45.9/1000 in Saudi Arabia and is one of the highest in the world [3,10]. The need for considerable improvement in the available maternal and perinatal facilities [10–14] which are currently inadequate [10,11] cannot be gainsaid. Other estimates [3,15–17] have also shown that children under the age of 15 years constitute about 50% of the Saudi population, and the fact that children under the age of 12 years constitute 45% of the total admissions into KKUH in the present study, agree with such estimates. The medical needs of this large pediatric population also deserve appropriate attention.

The prevalent diseases among our patients differ significantly from what currently exists in other developing countries. Gastroenteritis, malnutrition and the various specific infections such as measles, tetanus, tuberculosis, malaria and typhoid which are major causes of morbidity and mortality in most of the developing countries [18–22] are not prominent in the present series. It is unlikely that this is due to selectiveness, because as already noted, KKUH operates an open door 24-hour emergency service from where deserving cases are automatically admitted into the wards. An earlier report [23] indicated that the diseases which are rare in the present review were not uncommon in Riyadh around ten years ago. The changes observed were therefore very likely due to the rapid changes in the socioeconomic fortunes of Saudi Arabia and the phenomenal improvements in the country's welfare services during the recent past [1–3]. The almost total eradication of protein calorie malnutrition is attributable to the very high per capita income and the fact that food and other essential items are subsidized by the government [1]. Access to safe potable water and hygienic waste disposal is enjoyed by 95% and 88% of the population, respectively [1] and these together with the very impressive immunization coverage rates of 90% for DPT, polio and tuberculosis and 89% for measles have virtually eradicated these communicable diseases [2].

One current prevalent nutritional problem among Saudi children are rickets which were diagnosed in 61 children in the present series. This unusual prevalence of rickets in an environment where it is sunny year round has been shown to be due to seclusion of mothers and their infants from sunlight by the traditional housing designs, and also to the traditional Saudi custom of swaddling their infants [24,25].

The high frequency of congenital and heredofamilial disorders in the present analysis reemphasizes the paramount role of genetic factors in the pathoetiology of diseases in Saudi Arabia and other Middle Eastern countries. Several previous studies have shown that congenital abnormalities are the most frequent causes of perinatal deaths in the Kingdom [11-14] while other reports have emphasized the contributions of heredofamilial factors to the pathoetiology of various childhood disorders [7,9]. The high consanguinity rate involving 55% to 65% of all marriages in the country [3,17] is no doubt a very important factor in this regard. The need for increased attention to genetics and genetic counselling as important components of medical and pediatric practice in the Kingdom cannot be overemphasized. A National Institute for Research in Human Genetics is also highly desirable.

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ESTABLISHMENT OF A NORMAL REFERENCE RANGE FOR ADENOSINE DEAMINASE IN PLASMA OF HEALTHY SAUDIS USING THE CONTINUOUS SPECTROPHOTOMETRIC METHOD

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تم تقدير مستوى نازعة أمين الأدينوزين (EC ٣,٥,٤,٤) في بلازما ٣٨٩ من الذكور الأصحاء و٤٩٣ من الإناث الصحيحات بهدف وضع مرجع للمدى الطبيعي لدى السعوديين. وباستخدام طريقة قياس الطيف الضوئي المستمر، تم حساب مدى المرجع بطريقتين: باستخدام المتوسط ± ضعف الانحراف المعياري وباستخدام الحدود المئوية ٢,٥٪ - ٩٧,٥٪. لوحظ في الطريقتين أرتفاع بسيط في المدى لدى الأطفال بالمقارنة مع الكبار. أدخلت طريقة الحدود المئوية ٢,٥٪ - ٩٧,٥٪ جميع نسب الأشخاص تقريبًا ضمن المدى المقبول بين ١١,٥ - ٢٥ وحدة/ لتر. بلغ المدى الطبيعي لنازعة أمين الأدينوزين في الدراسة الحالية مقدرًا بالوحدة في الليتر ١٥-٢٣,٢٪ لإجمالي السكان، ١٤,٨ - ٢٣,٦ لجميع الذكور، ١٥,٠ - ٢٣,٠ لجميع الإناث و ١٦,٧ - ٢٤,٦ لجميع الأطفال. نناقش هذا المدى على ضوء الاختلاف الواضح في النتائج التي حصلنا عليها باتباع طريقتي الحساب المذكورتين والتوصية بطريقة ملائمة للسعوديين الأصحاء وهي طريقة الحدود المئوية ٢,٥٪ - ٩٧,٥٪. وتبرز هذه الدراسة أيضًا أختيار طريقة «اليس» و «غولدبيرغ» للمناظرة الحركية المستمرة لتقدير مستويات نازعة أمين الأدينوزين في البلازما.

The level of adenosine deaminase (EC. 3.5.4.4), was estimated in plasma of 389 healthy males and 493 healthy females in order to establish a normal reference range for Saudis. Using the continuous spectrophotometric method, the reference ranges were calculated in two ways using the mean ± 2 SD and the 2.5th – 97.5th percentile value methods. In both methods of calculation, a slightly higher range was observed for children as compared to adults. The method of 2.5th – 97.5th percentile values brought almost all of our subjects within the recommended range of 11.5 – 25 U/l. In the current study, the normal range for adenosine deaminase totalled 15.0 – 23.2, 14.8 – 23.6, 15.0 – 23.0 and 16.7 – 24.6 U/l for the overall population, all males, females, and children, respectively. The ranges are discussed in the light of significantly different results obtained by the two calculation methods and recommendation of an appropriate method for healthy Saudis, namely the 2.5th – 97.5th percentile values. The choice of the Ellis and Goldberg kinetic continuous monitoring method for the estimation of plasma ADA levels in the current investigation is also hereby justified.

Adenosine deaminase (ADA; EC 3.5.4.4), is a widely distributed enzyme which catalyses the deamination of adenosine into inosine and ammonia in the purine catabolic pathway. The enzyme is essential for the differentiation of lymphoid cells, particular T cells [1], and maturation of monocytes to macrophages [2]. Its deficiency in lymphocytes results in severe combined immunodeficiency disease [3,4]. Elevated adenosine deaminase activity is found in serum of patients with infectious mononucleosis [5], typhoid fever [6], liver diseases [7,10], acute leukemia [8], and sarcoidosis [19]. In recent years, clinical interest has focused on the enzyme assay in pleural fluids [12]. In pleural effusions of patients with tuberculosis, empyema, and rheumatoid pleural effusion, higher ADA

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activities are reported than for malignant or parapneumonic pleural effusions [9,11,13,14]. The normal reference range of serum ADA as reported in the literature is 11.5 – 25 U/l [15].

Because of the diagnostic accuracy of any test, and the decision of whether a person is healthy or unhealthy depends on the "normal reference values," it is essential to accurately determine the reference range for each parameter in each population [16]. Several environmental and genetic factors also play a role in modifying the normal ranges and the methods used for the determination significantly influencing the normal range.

We initiated this study to establish a normal reference range for ADA in male and female Saudis of different ages, using a kinetic continuous monitoring spectrophotometric method in preference to other methodologies. This article reports our findings and discusses the significant differences encountered between our population and the results quoted in literature. The choice of method for the enzyme assay is also justified.

Material and Methods

Subjects and Samples

The subjects of this study were all healthy Saudi individuals selected by a "two stage unit" statistical sample plan to cover a randomly distributed population in the Kingdom, thus ensuring population stratification. Blood samples were collected from adults and children attending schools, colleges, blood banks, hospital outpatient clinics, and primary health care units. All volunteers were interviewed and examined by a physician and their clinical history was recorded on special forms. An informed consent was obtained from each individual and parent of child. Only healthy subjects with no apparent signs of any illness were included in the study. The final group was composed of 389 male and 493 female volunteers.

Blood samples were collected in heparinized tubes and the plasma was carefully removed from the cells after centrifugation and stored frozen until required for analysis. The enzyme was shown to be stable at –20°C for three months [15].

Enzyme Assay

Adenosine deaminase was assayed in plasma by the continuous monitoring method of Ellis and Goldberg [15]. Plasma (100 μl) was incubated with 0.25 M phosphate buffer pH 7.5 (2.43 ml), 0.2 M 2-oxoglutarate pH 6.9 (30 μl), 15 mM NADH disodium salt (40 μl), glutamate dehydrogenase (450 U/ml, 50 μl), 20 mM ADP trisodium salt (50 μl), and distilled water (100 μl), at 37°C for ten minutes. The amount of endogenous ammonia present in the reagent and plasma was estimated by monitoring the change in absorbance of the above incubation mixture at 340 nm. To estimate the amount of ammonia liberated as a result of enzyme activity, 300 mM adenosine (200 μl) was added to the above mixture after a lag phase of three minutes and the change in absorbance monitored at 340 nm for ten minutes at 37°C.

Results

The laboratory results of the 882 subjects were carefully checked for thoroughness, coded and fed into the IBM PCXT computer for analysis using the SAS (Statistical Analysis System) software.

Table 1 summarizes the statistics and reference ranges (means ± 2 SD and the 2.5th – 97.5th percentiles) in males and females of various age groups and for all males, females, and the total population. The population was divided into six age groups, 1–14 years, 15–24 years, 25–34 years, 35–44 years, and 55+ years and the mean, median standard deviation (SD), and the reference ranges were calculated. The difference between males and females in each age group and between total males and females was determined by means of the student t-test. A *P* value of 5% or less was considered significant and the results in Table 2 shows no significant variations in the ranges of both sexes. However, slightly higher means of 20.4 and 20.5 U/l were observed in all children (< 5-years-old), and females over the age of 55 years, but this observation did not represent a significant difference between ages.

Figure 1 shows the frequency distribution histogram of ADA in all males and females and Figure 2 shows the same for all children (< 15 years) and adults (> 15 years). Both histograms depict Gaussian type distributions in both males and females and between children and adults which in turn predicts a straight line normal probability plot.

TABLE 1. *The descriptive statistics and normal reference range for adenosine deaminase in healthy Saudi subjects.*

						Reference range		
Age	Sex M/F	No. of cases	Mean U/l	Median U/l	S.D.	Mean 2SD ± U/l	U/l 2.5th–97.5th percentile	*P*-value
0–14	M	121	20.4	20.3	5.5	20.4 ± 11.0	16.2–25.1	0.93
	F	117	20.5	20.7	5.1	20.5 ± 10.2	17.1–24.0	
15–24	M	77	19.1	19.8	6.1	19.1 ± 12.2	14.9–24.1	0.27
	F	142	18.2	17.7	5.5	18.2 ± 11.0	14.5–22.2	
25–34	M	68	17.4	16.9	4.7	17.4 ± 9.4	13.1–20.6	0.5
	F	103	17.9	17.4	5.9	17.9 ± 11.8	14.5–21.7	
35–44	M	52	17.9	17.4	5.9	17.9 ± 11.8	13.8–22.7	0.88
	F	62	17.7	18	5.9	17.7 ± 11.8	14.3–21.5	
45–54	M	34	20	21	6.8	20.0 ± 13.6	12.2–25.2	0.38
	F	45	18.7	17.4	5.8	18.7 ± 11.6	14.0–23.8	
55 ±	M	37	18.6	18.6	6.7	18.6 ± 13.4	13.1–23.6	0.26
	F	24	20.5	21	6.1	20.5 ± 12.2	16.0–26.3	
Total	M	389	19.1	18 8	5.9	19.1 ± 11.8	14.8–23.6	0.44
	F	493	18.8	18.3	5.7	18.8 ± 11.4	15.0–23.0	
Grand Total	M + F	882	18.9	18.8	5.8	18.9 ± 11.6	15.0–23.2	

S.D. = standard deviation.

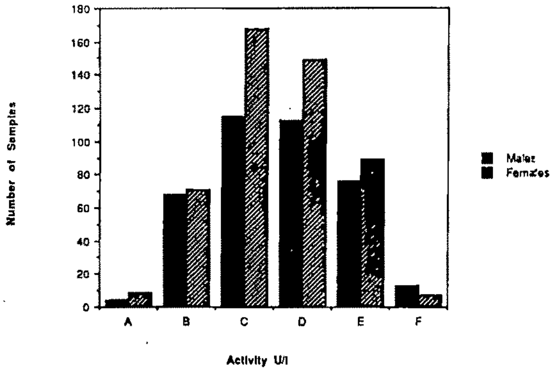

FIGURE 1. Frequency distribution histogram of adenosine deaminase (ADA) in healthy Saudi males and females.

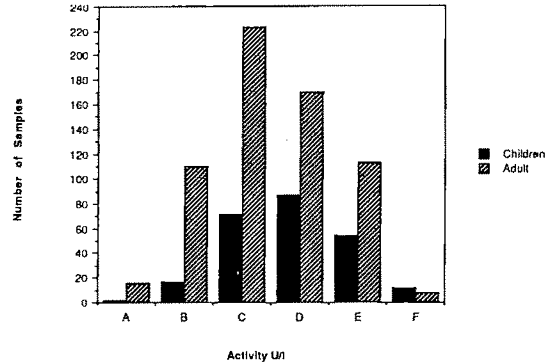

FIGURE 2. Frequency distribution histogram of adenosine deaminase (ADA) in children and adults.

TABLE 2. *Cummulative frequency distribution of reference ranges in six age groups for males and females.*

CMM	Males	Female
A = 2.4 – 7.4	4	9
B = 7.5 – 12.9	68	71
C = 13.0 – 18.4	115	168
D = 18.5 – 23.9	113	149
E = 24.0 – 29.4	76	89
F = 29.5 – 37	13	7
Total	389	493

Discussion

The reference ranges obtained for the overall population, all males, females, and children using the mean ± 2 SD method were 7.3–30.5, 7.3–30.9, 7.4–30.2, and 9.8–31.3 U/l, respectively. On the other hand, the reference range obtained for the overall population, all males, females, and children, using the 2.5th–97.5th percentile method were 15.0– 23.3, 14.8–23.6, 15.0–23.0, and 16.7–24.6, respectively. In both methods of calculation, a slightly higher range was observed for children as compared to adults, reflecting the slightly higher means observed in children in Table 3. As shown in Table 1, the difference between ages was not significant at 5%. The slightly higher means in children were not observed in the histogram (Fi-

TABLE 3. *Cummulative frequency distribution of reference ranges in six age groups for children and adults.*

CMM	< 15	> 15
A = 2.4 - 7.4	2	15
B = 7.5 - 12.9	16	110
C = 13 - 18.4	71	223
D = 18.5 - 23.9	87	170
E = 24 - 29.4	54	113
F = 29.5 - 37	12	8
Total	242	639

gure 2), the shape of which reflects a difference in population size rather than mean. Such is also the case with Figure 1 which depicts the difference in population size rather than a higher mean for females.

When compared with the recommended literature range of 11.5–25 U/l [15], the range obtained with the mean ± 2 SD method had lower values than the lower end of the recommended range owing to the influence of a high standard deviation ranging from 9.4–13.6. If this method was used for our subjects, most would be significantly lower than the recommended low of 11.5 U/l. On the other hand, the range which was calculated with the 2.5th–97.5th percentile method brought all of our subjects within the recommended range of 11.5–25 U/l, with the only exception of 24 females over the age of 55 years who exceeded the maximum value by 1.3. Thus, the ranges calculated from this study using the 2.5th–97.5th percentile method are recommended as normal reference ranges for ADA in healthy Saudis.

The establishment of a normal reference value for plasma ADA is of great clinical relevance. This is because plasma ADA activity increases in a whole variety of diseases including acute pneumonia, sarcoidosis, empyema, malignant neoplastic disease, rheumatoid arthritis, congestive heart failure, and liver disease [7,10,13,20,21]. In a recent survey [13], it was shown that ADA plasma levels of patients with pneumonia, malignant neoplastic disease, rheumatoid arthritis, and congestive heart failure maintained an average of 19.5 ± 2.1, 20.7 ± 1.8, 17.9 ± 2.8, and 20.9 ± 4.8 U/l, respectively. However, patients with sarcoidosis and empyema showed higher ADA plasma levels of 37.0 ± 6.9 and 27.4 ± 4.3 U/l, respectively. Similar elevated levels of the enzyme (30.2 ± 1.4 U/l) were reported in patients with Mycoplasma pneumonia [21]. More recently, many workers have shown increased serum ADA levels in toxoplasmosis, AIDS, hepatitis B infection, and peritoneal tuberculosis [23–25]. In a recent study (in press), we showed that plasma ADA levels in Saudi patients with pulmonary tuberculosis averaged 36.2 ± 13.2 U/l (n = 67) which is significantly higher than the normal reference range established by this study.

Methods used for the determination of ADA activity in biological fluids include measurement of the decrease in absorbance at 265 nm as adenosine is deaminated into inosine [17], or the increase in absorbance at 293 nm caused by the conversion of inosine into uric acid catalyzed by nucleoside phosphorylase and xanthine oxidase [18]. The first method, although sensitive, can be adapted for continuous kinetic assay. The amount of material collected for assay is limited by its absorbance at 265 nm; and high substrate concentrations cannot be used. Furthermore, the method is subject to turbidity variations during assay. The second method has the disadvantage of requiring high endogenous levels of nucleoside phosphorylase relative to ADA. More popular and recent methods measure the amount of ammonia produced over a period of time as a result of adenosine deamination. In the most familiar of these methods, Guisti measured the amount of ammonia produced by the indophenol reaction [19]. However, the Ellis and Goldberg method adopted in this study has the advantage that the overall reaction can be followed by the rate of NADH consumption [15]. In addition, the method is more convenient, more accurate, reproducible, and less time consuming. More recently, serum ADA has been assayed using HPLC technology [22]. Although this method is most specific and sensitive, it would be difficult to run on a routine basis since it would be costly.

In conclusion, this study has established a normal reference range for plasma ADA in healthy Saudis using the kinetic continuous colorimetric method of Ellis and Goldberg [15]. The established reference range approximates the recommended reference range within the limits of experimental error.

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XANTHOGRANULOMATOUS PYELONEPHRITIS: KING FAISAL SPECIALIST HOSPITAL EXPERIENCE

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راجعنا الملامح السريرية الامراضية في ١١ حالة متتالية من التهاب الكلية والحويضة الحبيبي الأصفر. كان هناك سبعة ذكور وأربع أناث تراوحت أعمارهم بين ست سنوات وست وخمسين سنة، وكان متوسط أعمارهم ٣٤ عامًا. كان المرضى على جانب واحد في عشر حالات وعلى الجانبين في حالة واحدة. وصاحبه انسداد في المسالك البولية في ثماني حالات نتيجة لوجود حصيات كلوية أو حالبية (٥)، وتضيق حالبي (٢)، وسرطان في المثانة (١). كان أثنان من المرضى ممن اغترست لهم كلية لاصابة كلاهم الأصلية بالتهاب الكلية والحويضة الحبيبي الأصفر. ووجدت في أحدى هاتين الحالتين بؤرة صغيرة من سرطانة الخلايا الكلوية في أحدى الكليتين بالإضافة إلى إصابتهما كلتاهما بالداء النشواني. وقد كانت الموجودات الإشعاعية غالبًا غير وصفية. وتجري مناقشة هذه النتائج بايجاز على ضوء الملامح البارزة لهذا المرض المنشورة في الأدب الطبي.

Clinicopathologic features in a series of 11 cases of xanthogranulomatous pyelonephritis are reviewed. There were seven males and four females ranging in age from 6–56 years with an average age of 34 years. The disease was unilateral in ten cases and bilateral in one. There was associated urinary tract obstruction in eight cases due to renal or ureteric stones (5), ureteric stricture (2), and carcinoma of the urinary bladder (1). Two of the patients were renal transplant recipients in which native kidneys were involved by xanthogranulomatous pyelonephritis. In one of these cases, a small renal cell carcinoma was found in one kidney along with amyloidosis involving both kidneys. Radiologic findings were mostly non-specific. These findings are briefly discussed in light of the salient features of this disease as published in the literature.

Xanthogranulomatous pyelonephritis (XPN) is an uncommon sub-type of chronic pyelonephritis. Histologically, in addition to the usual chronic inflammatory cells, large numbers of macrophages with abdundant lipid laden cytoplasm are seen. Because of the lipid rich foamy histiocytes, the lesions appear golden yellow and may mimic renal neoplasms, especially renal cell carcinoma. The condition is almost always unilateral and usually results in a non-functioning kidney. In most of the cases, there is a bacterial infection associated with urinary tract obstruction which is usually due to renal stones. XPN is mostly seen in middle-age women although it may involve either sex at any age. The usual clinical presentation is that of severe toxemia, tender flank mass, and mild urinary tract symptoms. The diagnosis may be suggested preoperatively on the basis of clinical presentation and radiologic findings. In most of the cases, however, a definitive diagnosis is established only after pathologic examination of nephrectomy specimen [1–5].

The purpose of this study is to review our experience with XPN and briefly discuss some of the salient clinical and pathologic features of this disease with a brief review of the literature.

Material and Methods

A search was made for cases of XPN in the files of the Department of Pathology at King Faisal Specialist Hospital and Research Centre from January 1978 - December 1991. A total of 11 cases

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were identified. The medical records of nine of these cases were reviewed with regard to age, sex, mode of presentation, cause of urinary tract infection, urine culture results, side involved, therapy rendered, and follow-up. In the remaining two cases, slides were sent to us for consultation but detailed clinical information was not provided, although some details regarding age, sex, and clinical presentation were available. Histopathology reports and all available histologic sections as well as gross photographs of the nephrectomy specimens were reviewed in all 11 cases. Three cases in which material for electronmicroscopy was available, electronmicrographs were studied and correlated with light microscopic appearance. All available radiologic studies were also reviewed in detail.

Results

Clinical Features

There were nine adults and two pediatric patients with an average age of 34 years and male-female ratio of 1:1.2. Loin pain was the most frequent mode of clinical presentation. Urinary tract obstruction was present in 8 of 11 patients. Further clinical details are noted in Table 1.

Radiologic Findings

Radiologic studies were available in eight cases. Most of these revealed non-specific changes which were suggestive of the diagnosis. The details of these findings are noted in Table 2.

Calcification along the GU tract was present in 5 out of 8 cases. All cases (except Case 5 with focal

TABLE 1. *Clinical features of XPN cases.*

Case No.	Age/ Sex	Clinical presentation	Cause of urinary tract infection	Urinary tract infection	Side	Comments
1	35/F	Left groin pain bilateral renal calculi	Renal calculi	Klebsiella	Lt	Had parathyroidectomy for hyperparathyroidism.
2	56/M	Frequency, urgency, burning on voiding	Transitional cell carcinoma urinary bladder	Pseudomonas	Lt	Died from cerebral metastasis a year later.
3	55/M	Right loin pain	Ureteric stones	E. Coli	Rt	Doing well
4	24/F	Left loin pain	Stones at pelvi ureteric junction	No growth	Lt	Vesico-vaginal fistula following forceps delivery. Had bilateral ureterosigmoidotomy.
5	29/R	Loin pain and dysuria	No obstruction	E. Coli	Rt	Ultrasound revealed mass in Rt. upper pole. Partial upper pole nephrectomy.
6	50/M	Left loin pain	Stenosis of pelvi ureteric junction	No growth	Lt	Doing well
7	44/M	Abdominal distention	Bilateral staghorn calculi		Rt-Lt	Renal transplantation a year earlier. Renal cell carcinoma. Lt. kidney. Amyloidosis both kidneys.
8	35/M	Loin pain, bilateral	Ureteric strictures, bilateral	Klebsiella	Rt	Renal allograft 7 years earlier. Bilateral nephrectomy. Contralateral kidney showed chronic pyelonephritis.
9	41/F	Left loin pain	Renal stones	No growth	Rt	Well one year later.
10	6/F	Left loin pain	No obstruction	Not available	Lt	No follow-up
11	9/F	Right loin pain	No obstruction	Not available	Rt	No follow-up

TABLE 2. *Radiologic findings in 8 patients with XPN.*

No.	Site	IVP	U/S	CT	Comments
2	Left kidney	Initial IVP was was within normal limits.	–	Pelvis shows bladder mass	Follow-up studies showed non-visualization of left kidney.
3	Right kidney	Multiple calcifications in right kidney and right midureter. Non-functioning right kidney.	–	–	–
4	Left kidney	3 stones (2x3 cm in the left and 1 stone (1 cm) in the right kidney. Non-functioning left kidney.	–	–	No other investigations.
5	Upper pole right kidney	No calcification	Echo-poor mass upper pole	Low density lesion	Gallium Scan positive. Angiogram showed positive abnormal vessels at the periphery of a hypovascular mass.
6	Left kidney	No calcification seen	–	–	Non-functioning left kidney on renal scan.
7	Right kidney	Bilateral renal calcification in native kidney.	Bizarre looking mixed echogenicity	Irregular thick-walled cyst	Chronic renal failure. Transplant kidney was okay.
8	Bilateral kidneys	Calcification of the distal ureter bilaterally on the KUP film	Hydronephrosis bilaterally	Hydronephrosis hydroureter	Had renal transplant
9	Right kidney	Calcification on KUP film	Mixed mass cystic and solid	–	Non-functioning right kidney on renal scan.

lesion) showed renal mass with non-functioning kidney on the involved side.

Pathologic Findings

Gross Appearance

The resected kidneys were relatively small and somewhat shrunken (average weight 110 g) and showed prominent surface scarring. In Case 7 with bilateral nephrectomy, the right kidney weighed 1800 g and was markedly distended by greenish yellow turbid thick fluid. The left kidney weighed 382 g. In all cases, the renal pelvis and calyces were variably dilated and were lined by soft bright yellow material which extended into adjacent renal parenchyma, forming nodules of similar material (Figures 1 and 2). In eight cases, these changes were limited to the kidney while in the remaining three there was extension into perirenal adipose tissue. In one patient (Case 5), the lesion was limited to one pole. In the remaining cases, the entire kidney was involved by disease. In Case 7, in addition to the lesions of XPN, a 3.5 × 3 × 3 cm mass with gross appearance of renal carcinoma was noted.

Microscopically, the kidneys showed features of advanced chronic pyelonephritis with scarring and atrophy of the renal parenchyma. The calyces and renal pelvis were lined by an inflammatory exudate composed of large number of lymphocytes, plasma cells, and polymorphonuclear cells (Figure 3). In addition, there were large aggregates of histiocytes with abundant foamy cytoplasm (Figure 4). Variable numbers of multi-nucleated giant cells were also present.

In one case, these giant cells were especially

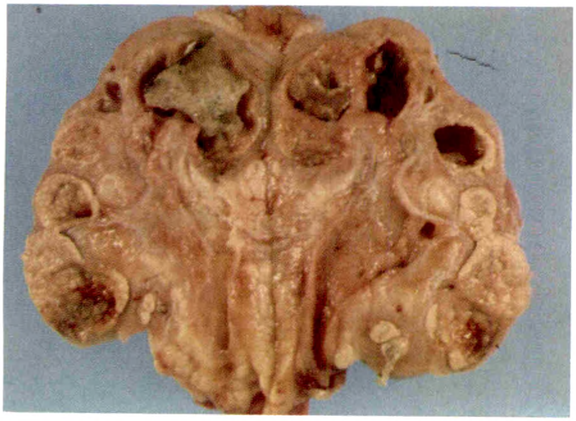

FIGURE 1. Photograph of a typical nephrectomy specimen with XPN featuring dilated calyces lined by soft yellow exudate. A staghorn calculus is also present.

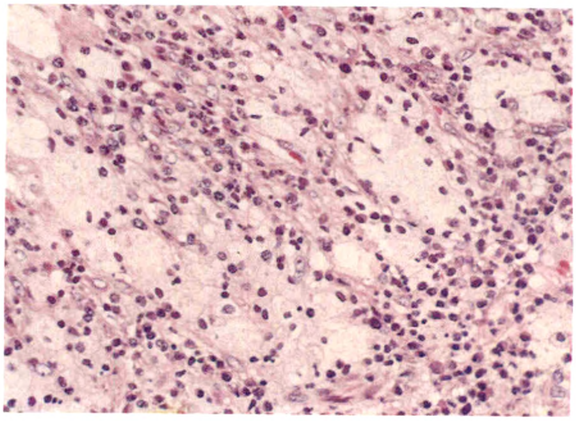

FIGURE 4. Higher magnification photomicrograph showing the inflammatory exudate predominantly composed of lymphocyte, plasma cells and larger numbers of histiocytes with foamy cytoplasm. (Hematoxylin and eosin stain, 250×.)

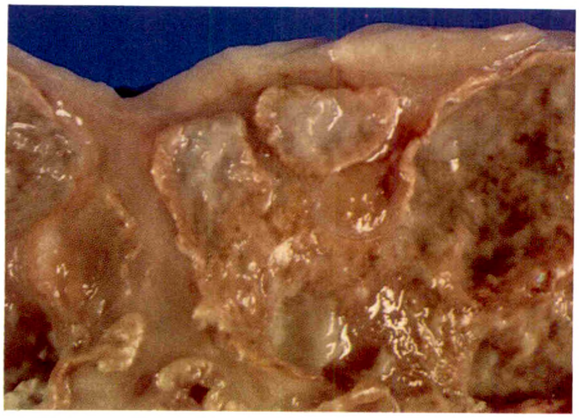

FIGURE 2. Close-up view of another kidney with extensive XPN. Dilated calyces are lined by soft yellow exudate.

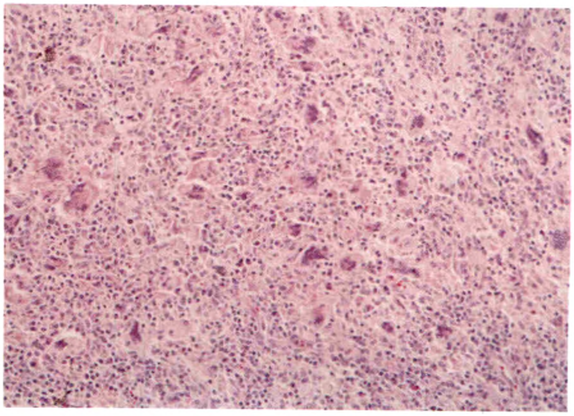

FIGURE 5. Photomicrograph showing an area within the inflammatory infiltrate showing lymphocytes, plasma cells and larger numbers of multi-nucleated giant cells. (Hematoxylin and eosin stain, 150×.)

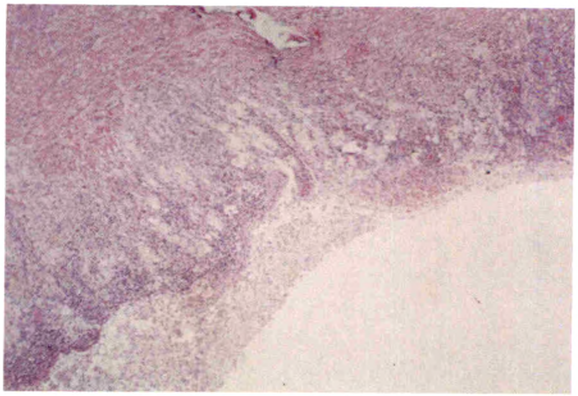

FIGURE 3. Low power photomicrograph showing dilated calyces lined by inflammatory exudate. (Hematoxylin and eosin stain, 80×.)

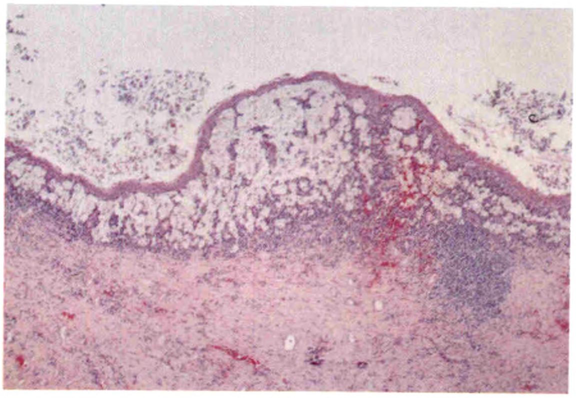

FIGURE 6. A dilated calyx lined by metaplastic squamous epithelium and showing aggregates of histiocytes with foamy cytoplasm. (Hematoxylin and eosin stain, 100×.)

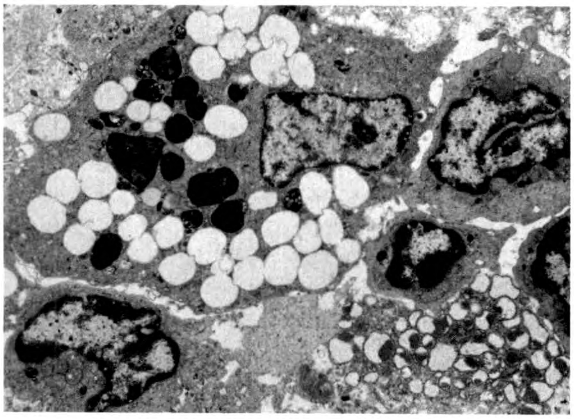

FIGURE 7. Electronmicrograph showing histiocytes with abundant vacuolated cytoplasm. No bacteria are present. (Uranyl acetate and lead citrate stain, 5,000×.)

numerous (Figure 5). The lining transitional epithelium of the renal pelvis and calyces was extensively ulcerated in areas of the inflammatory infiltrate. In two cases, it was replaced by squamous epithelium (Figure 6). In all cases, the renal parenchyma revealed extensive damage associated with loss of tubules and replacement by fibrosis. Variable cystic dilatation of tubules was also seen. In one patient, Case 7, in addition to XPN, the left kidney revealed a nodule composed of renal cell carcinoma. In this kidney, multiple microscopic tubular adenomas were also present. In this case, both kidneys were involved by XPN and in addition revealed amyloidosis involving glomeruli, blood vessels, and perirenal adipose tissue. Presence of amyloidosis was confirmed by congo red staining and demonstration of birefringence under polarized light.

Electronmicroscopy Findings

In three cases, electronmicroscopy of the XPN lesions revealed a mixture of polymorphonuclear cells, lymphocytes, plasma cells and a large number of macrophages. The latter revealed abundant cytoplasm full of lipid vacuoles, some of which contained myelin figures. No bacteria within the cytoplasm or intercellular spaces were noted (Figure 7).

Discussion

Xanthogranulomatous pyelonephritis (XPN) was first recognized in 1916 by Schlagenhaufer as a distinct clinicopathologic entity [5]. In 1934, Putschar described additional cases and emphasized the presence of foamy histiocytes [5]. The term xanthogranulomatous pyelonephritis was first suggested by Osterline in 1944 (reference 5). Several individual case reports as well as several small and large series of cases have since been reported [1–5].

The pathogenesis of XPN is not fully understood, although several mechanisms have been suggested. Most of the causes of XPN are associated with obstruction of the urinary tract and infection by an organism of low virulence. In a majority of the cases, the infecting organism is a gram negative bacillus, most often E. coli or Proteus mirabilis. Other organisms include Kliebsiella, Providencia and Staphylococcus aureus [1–5]. The lesions of XPN have also been produced experimentally by ligating the ureter in rats followed by intravenous injection of E. coli. About a month later, lesions closely resembling XPN may be seen [6]. Thus, it appears that obstruction of the urinary tract and low grade infection of the kidney may lead to the development of XPN.

The obstruction of urinary tract in a majority of the cases of XPN is due to renal calculi. In some cases, the obstruction may be secondary to a neoplasm involving the renal pelvis, ureter or urinary bladder. Several histologic types of tumors have been described including transitional cell papillary carcinoma of the bladder and ureter, mucinous carcinoma of the renal pelvis and adenocarcinoma of the urinary bladder [7–10]. In our patients, 8 of the 11 cases had urinary tract obstruction which was due to renal or ureteric stones (5 cases), ureteric stricture (2 cases), and transitional cell carcinoma of the urinary bladder (1 case).

It is not clear how infection and urinary tract obstruction leads to accumulation of a large number of foamy histiocytes characteristic of XPN. In 1953, Freidenberg and Spjut [11] proposed an alteration of lipid metabolism with hypercholesterolemia. However, this theory is contradicted by almost constant unilateral involvement and the infrequent finding of hyperlipidemia. Arterial insufficiency was proposed by Saeed and Fine because the lesions of XPN are relatively avascular [12]. However, other lesions associated with relative lack of vascularity such as papillary necrosis are not associated with changes of XPN. Various lesions with phlebitis and thrombosis were incriminated by McDonald [13]. However, these lesions are inconsistent and are not always present. Hemorrhage is a frequent finding in XPN and some authors have suggested that lipid within the histiocytes is derived from the breakdown of erythrocytes. However, XPN lesions are usually devoid of any excess amount of hemosiderin, making such an explanation untenable. Parson et al [5] believed that the problem was one of destruction of peripelvic fat by infectious process so that lysed fat is taken by the macrophages. Others have suggested a block in lipid transport, lymphatic obstruction, reaction to specific infective agents, and altered immunologic competence [5].

The present series has several unusual features. First, the average age in our patients is 34 as opposed to 50 in most of the series. Second, seven of the 11 patients in our series were male whereas most of the previously published series show a preponderance of female patients. The significance of the difference is not clear, although sampling error due to a small number of cases in our series may be a contributing factor.

Another unusual feature of our series is that two of our patients were recipients of renal transplants in which XPN was encountered in the native kidneys. Such an occurrence has been documented in the literature in only one previously published case report [14]. In another two patients, XPN was involved in the renal allografts [15,16]. Thus, it appears that in a renal transplant recipient, native kidneys as well as the transplanted kidneys may develop XPN, although cause and effect relationship is highly unlikely.

The most unusual patient in our series was Case 7. This patient, a 44-year-old renal transplant recipient, developed bilateral XPN of native kidneys. In addition, there was amyloidosis in both kidneys and a small renal cell carcinoma in the left kidney. To the best of our knowledge, such a combination of pathologic conditions in one patient has not been previously reported. Bilateral XPN is extremely rare with only seven cases reported in the literature [16–22]. Similarly, association of XPN with amyloidosis has been reported in only two patients [23,24]. Renal cell carcinoma in association with XPN is also rare with only 11 previously reported cases [23–32].

A significant aspect of pathology of XPN is that the foamy histiocytes invariably present in these lesions may be mistaken for clear cells of the renal carcinoma. Indeed, two of the cases included in our series were received for consultation after a diagnosis of renal carcinoma was rendered at the referring hospital. This would indicate that in spite of the fact that this disease has now been recognized for several decades, confusion with renal carcinoma continues to be a problem. This is because XPN is a relatively uncommon disease so that an average pathologist may not encounter a case in many years and thus may not be fully familiar with this condition. It is hoped that this paper will help to elucidate and highlight the clinical and pathologic spectrum of this interesting disease.

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KOHL–THE TRADITIONAL EYELINER: USE AND ANALYSIS

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الكحل هو مزيج مسحوق يستخدم لتجميل العينين ولمعالجة أمراض العيون في عدد من بلدان الشرق الأقصى والأوسط. قمنا بدراسة استعمال الكحل لدى ٣٦٠ شخصًا اختيروا عشوائيًا من منطقة الرياض. استخدم الكحل من قبل ١٣٪ من الذكور و ٢٦٪ من الإناث، وعلى الأخص من قبل الأميين والمسنين. استعمل ٤٠٪ من الأمهات الكحل لأطفالهن في الشهر الأول بعد الولادة. أظهر تحليل خمس عينات تجارية من الكحل احتواء بعض هذه المستحضرات على درجة مرتفعة من pH (قلوية) ومن تركيز الرصاص (٨٨٪)، الأمر الذي يشير إلى تحضير غالبية هذه المواد من الرصاص وليس من الاثمد (الانتيمون). ومن المثير للأهتمام أن لبعض مستحضرات الكحل تأثيرًا ضعيفًا ضد بعض الجراثيم كالعقديات والعنقوديات والمتقلبات. لا يزال استعمال الكحل القائم على الرصاص ممارسة شائعة وخطيرة يجب التنفير منها وبخاصة لدى الأطفال. إن استقصاء الدور الذي يؤديه استعمال الكحل التقليدي في إحداث أمراض العيون الخارجية الشائعة في أقطار الشرق الأقصى والأوسط لأمر يستحق الدراسة.

Kohl is a traditional powder-like mixture used as an eyeliner and to treat eye disease in many Middle and Far East countries. We studied kohl use among 360 individuals selected at random in Riyadh, Saudi Arabia. Kohl was used by 13% of males and 26% of females, especially the elderly and illiterate. Forty percent of females with children applied kohl to the eyes of their children during the first postnatal month. Analysis of five commercially available traditional kohl samples showed that some preparations have a high pH and a high lead concentration (88%), indicating that most preparations are lead-based rather than antimony-based. It is interesting to find that some kohl preparations have a weak antimicrobial effect against *Streptococcus, Staphylococcus* and *Proteus* species. The use of lead-based kohl is still a common and serious practice and should be discouraged, especially in children. The role of traditional kohl use in the pathogenesis of common ocular external diseases prevalent in Middle and Far East countries merits investigation.

Kohl has been known and used traditionally in the Middle and Far East as an eyeliner since antiquity. It has been used as a cosmetic by women and some men and has even been applied to the eyes of children and umbilicus of newborns. Kohl has been used also for treating and preventing ocular diseases.

Pure kohl contains antimony sulfide and trisulfide as its main constituents. The source of kohl is a shiny, dark stone known in Arabic as "ithmed", which translates to antimony in English. In Urdu, the word "surma" refers to both antimony and kohl.

Ithmed may be ground to a powder ready for use as an eyeliner. Kohl may comprise ithmed alone, or in combination with other materials such as camphor, menthol, almond seeds, essence wood, or ash. Due to the scarcity of ithmed, many manufacturers have substituted galena (lead sulfide), which has almost the same color and shiny surface as ithmed. Other manufacturers add charcoal or other vegetable ashes to the preparation. This has resulted in a wide variety of commercially available preparations, either in the form of stone, powder, finger rods, or pencils.

Several reports have implicated kohl as the cause of lead poisoning among children [1–4].

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Blood lead levels of children using kohl were found to be much higher than those of European children who did not use kohl [4]. Samples of kohl available in Saudi Arabia have also been studied for their microbial content and were found to be heavily contaminated with *Bacillus* species, gram-negative bacilli, and a number of fungi [5]. In addition, Hannan et al analyzed various commercial brands of kohl for potential carcinogens and have classified both mutagenic and non-mutagenic preparations [6]. The investigators found that brands lacking mutagenic properties were mostly antimony-based and contained no organic material.

There are no reports on the prevalence of traditional kohl use and the sociocultural basis for its use. The antimicrobial effect of kohl has not yet been reported. In order to investigate this important public health problem, we undertook the following study.

Patients and Methods

We selected at random 360 individuals, including patients attending King Khaled Eye Specialist Hospital (KKESH) during the period of October - December 1988, patients' relatives, and employees working at the hospital. Individuals were asked to respond to a multiple-choice questionnaire on age, sex, marital status, education, use of kohl, and whether kohl was ever applied to the eyes of children or infants in the household.

Chemical Analysis of Kohl Samples

Five of the most commonly used preparations of traditional kohl were selected and purchased from the local market. The preparations were stone kohl and the following powder forms: Ka-Noor, kohl Noori (imported from India), brown kohl, and kohl Samah (made locally in Saudi Arabia). We also selected at random one of the commonly used modern pencil eyeliners (an Italian product) for comparison. An equal weight of each preparation (20 mg) was prepared for analysis in powder form by grinding the stone and pencil forms. A standard weight was then tested for pH and solubility in water. The pH value of two samples (one traditional kohl preparation and the modern eyeliner) was not determined because of the waxy nature and water insolubility of the samples.

Lead and antimony concentrations in all six specimens were measured using electrothermal atomic absorption spectrophotometry at King Faisal Specialist Hospital and Research Centre laboratories, Riyadh. An accurately weighed amount of each specimen (i.e., 10 mg) was digested with 10 ml of concentrated nitric and sulfuric acids, (1:1, by volume), and the dried residue was ashed for six hours. The ash was dissolved in 2 ml of 0.05% nitric acid in deionized water by sonication for two minutes to yield absorbance values within the linear range for each element, then 10 μl was injected into the graphite furnace by the autosampler. The operating conditions of the instruments used were those recommended by the manufacturer (Varian Techtron Pty, Mulgrave, Victoria, Australia).

Antimicrobial Effect of Kohl

A 0.5 MacFarland standard suspension of bacteria was spread evenly over a 150-mm plate of Mueller-Hinton agar in the same manner used for antibiotic susceptibility testing. A 2 mm well was made in the agar in which 5 mg of kohl powder was placed. Plates were incubated in a non-CO_2 incubator at 35°-37°C for 18 to 24 hours. Other plates were incubated in a CO_2 incubator at room temperature.

The effects of kohl on bacterial growth was graded according to the size of inhibition zone of bacterial growth around the kohl well. Absence of inhibition zone indicated no evidence of susceptibility, spotty growth within a small zone surrounding the kohl inoculum indicated slight inhibition, while a true sensitivity zone of no growth surrounding the kohl inoculum indicated susceptibility.

Results

There were 120 male and 240 female patients. Age and sex distribution is shown in Table 1. Ninety percent of the males were illiterate; of the females, 31% were illiterate, 28% had a secondary school education or less, and 41% had a university education.

Sixteen males (13.3%) and 62 of the females (25.8%) were using traditional kohl; the other females were using modern eyeliner. Five percent (3/56) of females below the age of 20 years, 19.6% (22/118) of the middle-age females (20–40 years), and 56.0% (37/66) of the older females (above 40 years) used traditional kohl regularly. The use of traditional kohl was found more prevalent among illiterate females; 46 of 74 illiterate females (62.2%) compared to 8/61 (13.1%) of the females with elementary or secondary school education, and 8/97 (8.2%) of university educated females. This was found statistically significant when a chi-square analysis was performed ($\chi^2 = 70.138$ on two degrees of freedom, $P < 0.0001$).

All the males and 38% of the females using traditional kohl applied it to the conjunctival cul-de-sac and the rest of females applied it to the lid margin. None of the males and 18% of the females shared the use of kohl from the same container.

The frequency of kohl use among females and males of all age groups is shown in Table 2. The reasons given by users for traditional kohl use among males and females are shown in Table 3. When individuals were asked if they had any redness, irritation or problems related to the use of kohl, 18% of females answered positively and all males denied any problems. Fourteen of the females using traditional kohl wear contact lenses. Seven of them had ocular irritation related to the use of kohl, which disappeared when kohl use was discontinued.

Ninety-nine of the surveyed females have children and 40 (40.4%) had applied kohl to their children's eyes in early childhood. Of these, 62.5% (25/40) had applied kohl to the neonate eyes in the first postnatal week and 35.0% (14/40) had done so sometime during the first postnatal month.

Chemical Analysis

The pH range of the four tested kohl preparations was 6.10 to 10.90, and the solubility of the four samples in water was slight (0.02–0.03%). The contents of each of six samples tested for lead and antimony are shown in Table 4.

Antimicrobial Effect

The antimicrobial effect study of kohl samples has shown that Sample No. 1, the black stone kohl, had a slight inhibition zone for the growth of *Proteus vulgaris* and *Staphylococcus aureus* and a good inhibition zone (8 mm) for growth of *Streptococcus pyogenes*. Sample No.2, Kohl Ka Noor, had a slight inhibition zone for the growth of *S. pyogenes*. Sample No. 4, brown powder kohl had a slight inhibition zone for both *S. pneumonia* and *S. pyogenes*. No antimicrobial effects were found for the other samples.

TABLE 1. *Age and sex distribution of the study sample.*

		Males	(%)	Females	(%)
Total no.	360 (100)	120	33	40	67
Age					
< 20 years	72 (20)	16	13	56	23
20–40 years	166 (46)	48	40	118	49
> 40 years	122 (34)	56	47	66	28

TABLE 2. *Frequency of kohl use.*

	Males	Females
Once daily or more	50%	73%
One to four times weekly	13%	15%
Rarely	37%	12%

TABLE 3. *Reasons for using kohl.*

Reason (No.)	Males (16) No.	(%)	Females (62) No.	(%)	Total (78) No.	(%)
Cosmetic (1)	4	(25)	50	(80.6)	54	(69.2)
Improve vision (2)	8	(50)	3	(4.8)	11	(14.1)
Prophylaxis (3)	0	(0)	0	(0)	0	(0)
Therapeutic (4)	0	(0)	1	(1.6)	1	(1.2)
Religious belief (5)	0	(0)	2	(3.2)	2	(2.6)
Nos. 1 and 5	0	(0)	2	(3.2)	2	(2.6)
Nos. 2 and 5	4	(25)	2	(3.2)	6	(7.7)
No answer	0	(0)	2	(3.2)	2	(2.6)

TABLE 4. *Lead and antimony contents of different kohl preparations.*

Sample no.	Kohl brand	Lead (%)	Antimony (%)
1	Black stone	88	0
2	Ka-Noori	4.1	0.53
3	Kohal Noori	3	1.82
4	Brown powder	traces	1.13
5	Samah powder	20	9.97
6	Pencil eyeliner	0	2.09

Discussion

Although many women moved to the use of eyeliner as a result of public education programs and improved educational and socioeconomic status, traditional kohl continues to be used by many women and men in Saudi Arabia, especially among the elderly and illiterate. There is a false belief that all commercially available kohl is "ithmed," that is, antimony-based. Prophet Mohammed (PBUH), Peace Be Upon Him, had advised Moslems to use kohl originating from ithmed. Such a religious reason is an important factor for its common use among women and men and for its application to children's eyes.

It is not surprising to find that the main reasons for kohl use among males is to improve vision. Lid surfaces tinted by such a black, shiny powder will result in more reflection of the incident light rays and, therefore, glare will be decreased. This is noticed particularly by males who are more exposed to the bright sun than the females who usually wear veils. It is interesting to note that 25% of males used it for cosmetic reasons.

The most serious aspect of kohl use is its application to children's eyes and umbilicus. Added to the risks of ocular infection and septicemia due to contamination [5], application of lead-based kohl may lead to chronic lead poisoning if the kohl is absorbed from the nasolacrimal mucosa or by ingestion through sucking the contaminated fingers [7]. Such a practice is still followed by many women (40% in our study), even by those who do not use traditional kohl. Chronic lead poisoning can result in hypochromic and microcytic anemia, chronic encephalopathy, and renal damage [8]. Lead absorption has been found to be greater in children than in adults [9]. In addition, previous studies have reported that asymptomatic lead poisoning may cause significant and permanent impairment of the nervous system functions [10].

Frequent use of preparations with high-alkaline pH values is irritating to the corneal and conjunctival surface and will increase the risk of infection by breaking the continuity of the corneal and conjunctival epithelial layers, and by changing the tear pH, making it favorable for growth and adherence of various ocular pathogens on the ocular surface. There is poor solubility of kohl particulate in water; active substances in kohl, whether organic or inorganic, are therefore deposited on the conjunctival surface, the mucous membrane lining the nasolacrimal system, and in the upper gastrointestinal tract. The role of kohl in precipitating nasolacrimal duct obstruction is possible and should be studied.

One strong belief of Middle Easterners is that kohl (ithmed) protects from and treats eye infections. It is interesting to find that some preparations of kohl have a weak antimicrobial effect. The antimicrobial effects of three preparations of kohl (Samples 1, 2, and 4) are mostly minimal with a slight inhibition zone, except against *Streptococcus pyogenes*, where an 8 mm inhibition zone was elicited. Such antibacterial effects can be explained by the high pH of these preparations. Kohl Sample No. 1 (black stone) has an antibacterial effect on three different organisms which may be explained by its high lead content (88%). It may be that the presence of other metals and organic substances in kohl play a role in the antibacterial effect. This finding, however, does not justify the use of kohl with its documented contamination. Such a finding may explain in part why using contaminated kohl does not cause significant clinical conjunctivitis among most of the users.

In conclusion, kohl use is still a significant and serious public health problem in our community. Most commercially available kohl preparations in Saudi Arabia, which are also available in other Middle Eastern countries, are risky to use due to product contamination, high pH, and high concentrations of lead. Kohl use in children can lead to very serious general and ocular complications. Kohl may play a role in the external eye infections by its contamination and shared use. The role of kohl in the pathogenesis of some ocular surface diseases and infections prevalent among kohl users merits further study. Public education programs for this problem are needed, as well as government health policies for the control of importing and selling cosmetic eye products to the public.

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LACTASE DEFICIENCY IN PATIENTS WITH INTESTINAL SCHISTOSOMIASIS

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تم تقييم حالة ٦٠ مريضاً يعانون من الخمج بالمنشقات المنسونية لتقصي عوز اللاكتاز وذلك باتباع طرق متنوعة بما في ذلك طريقة مقايسة اللاكتاز في الخزعات المعوية. كان ثلاثون مريضاً يشكون من داء كبدي معوي بالمنشقات وهم المجموعة الثانية وتمت مقارنة حالاتهم مع مجموعة ضابطة قوامها ستون شخصاً وهي (المجموعة الثالثة). تم تقييم حالات عوز اللاكتاز بأعـراض عدم تحمل اللاكتوز، ودرجة حموضة البراز (PH)، والتركيز التناضحي، واختيار تحمل اللاكتوز بالفم، واختبار هيدروجين النفس بعد إعطاء اللاكتوز بالفم، ومقايسة نشاط اللاكتاز في خزعات معوية صغيرة. أظهر اختبار تحمل اللاكتوز بالفم عدم التحمـل في نسبة ٣٦,٧٪ من المجموعة الأولى و ٤٠٪ من المجموعة الثانية مقارنة بنسبة ٢٣,٣٪ في مجموعة الضبط. أمـا اختبـار هيدرجين النفس بعد إعطاء اللاكتوز بالفم فقد أظهر عدم التحمل بنسبة ٢٦,٧٪، ٣٠٪ و١٨٪ للمجموعات الثلاث على التوالي، وهو فرق ذو أهمية إحصائية بالنسبة للمجموعتين الأولى والثانية. سجلت الأعراض البطنية لنقص اللاكتاز معدلات مرتفعة في مجموعة المرضى مقارنة بجموعة الضبط وكانت أكثر ارتفاعًا في المجموعة الأولى مقارنة بالمجموعة الثانية. أما متوسط نشاط اللاكتاز (مقدرًا بوحدات مايكرومول لكل غرام من الوزن الرطب في الدقيقة) فلم يكن مرتفعًا من الناحية الإحصائية في المجموعة الأولى في حين أنه كان مرتفعًا في المجموعة الثانية بالمقارنة مع مجموعة الضبط. لم تظهر صلة بين نشاط اللاكتاز في الغشاء المخاطي وأعراض نقص اللاكتاز في المجموعة الأولى. توجد بالتالي عوامل أخرى قد تؤثر في تحلل (تموه) اللاكتوز في داء المنشقات المعوية. أظهرت الدراسة أيضًا أن اختبار هيدرجين النفس بعد إعطاء اللاكتوز بالفم هو الأكثر حساسية ونوعية وفاعلية بين الأختبارات غير الباضعة.

Sixty patients having schistosomiasis mansoni infection were studied for lactase deficiency by different methods including lactase assay in intestinal biopsies. Thirty patients suffering from simple intestinal (Group I) and 30 patients suffering from hepatointestinal (Group II) schistosomiasis were compared to 60 controls (Group III). Lactase deficiency was evaluated by symptoms of lactose intolerance, stool pH and osmolarity, oral lactose tolerance test (OLTT), oral lactose hydrogen breath test (OLHBT) and lactase activity (LA) in small intestinal biopsies. OLTT showed intolerance in 36.7% of Group I and 40% of Group II compared to 23.3% of the controls. OLHBT showed intolerance in 26.7%, 30% and 18% for the three groups respectively, indicating a significance in Groups I and II. Abdominal symptoms of hypolactasia had higher scores in the patient groups compared to the controls, and was even higher in Group I than Group II. The mean lactase activity measured by micromol/gm wet wt/min was not statistically higher in Group I but higher in Group II than the controls. No correlation was found between lactase activity in the mucosa and the symptoms of hypolactasia in Group I. Hence, other factors in intestinal schistosomiasis may affect lactose hydrolysis. The study showed also that OLHBT is the most sensitive, specific and efficient among the non-invasive tests.

Schistosomiasis, an endemic disease in Egypt, leads to malnutrition and portal hypertension. Malnutrition secondary to severe liver disease and poor dietary intake may cause malfunction of the small intestinal mucosa [1]. Pancreatic damage may affect its exocrine function [2] leading to malabsorption. Portal hypertension may lead to structural abnormalities in the small intestine

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[3,4]. This was attributed to edema and congestion of the mucosa [5,6]. Liver diseases may be accompanied by abnormal bacterial flora [7] which may lead to deconjugation of bile salts resulting in damage of the intestinal mucosa [8].

This may lead to deficiency in lactase responsible for hydrolysis of lactose into glucose and galactose [9]. Hence, symptoms such as abdominal distention, borborygmi and diarrhea may appear in schistosomiasis. The aim of this study is to evaluate lactase activity in intestinal and hepatointestinal schistosomiasis.

Patients and Methods

Three groups of patients were studied. Group I included 30 patients having simple colonic schistosomiasis. The diagnosis was based upon detection of *Schistosoma mansoni* ova in stools or in rectal or colonic biopsies examined by the transparency technique [10].

Group II was composed of 30 cases with hepatointestinal schistosomiasis. The diagnosis was confirmed by stained sections from the liver showing granulomata or by abdominal ultrasonography showing periportal fibrosis [11].

Group III; a control group was comprised of 60 normal healthy subjects with no apparent gastrointestinal disease, no history of schistosomiasis or hepatic disorders.

All subjects were subjected to full history, physical examination with stress on symptoms and signs of lactose malabsorption and laboratory investigations were done.

Three tests for lactose malabsorption were carried out; namely, lactose intolerance test, lactose hydrogen breath test and estimation of lactase activity in small bowel biopsies.

Oral Lactose Tolerance Test (OLTT)

OLTT was done by giving the subjects 50 gms of lactose powder dissolved in water. The glucose oxidase method was used [12]. Symptoms of intolerance including abdominal distention, meteorism, abdominal colic, flatus, borborygmi and diarrhea were rated according to the severity; 1 point if mild, 2 if moderate, and 3 if severe.

Biopsy of Small Intestine

Fiberoptic endoscopes were used to obtain jejunal biopsy (Olympus CIF XQ, GIF P, or JFB, gastroscope). The subjects remained at fast and diazepam 10 mg was given I.V. before the procedure [13].

Reaching the third part of the duodenum, cusped forceps with a central spike was introduced beyond the tip of the gastroscope to reach the duodeno-jejunal junction or the jejunum and blind biopsies were obtained. Two biopsies were obtained from each individual.

The intestinal lactase was assayed by Dahlqvist's method [14]. The specimens were weighed, homogenized in cold water to a concentration of 10 mg/ml and centrifuged. 0.1 ml of the supernatant was added to 0.1 ml of lactose solution and incubated in a water bath of 37°C for one hour, then removed; 0.5 ml of the solution was mixed with 3 ml of Tris-glucose oxidase (TGO) reagent and incubated for one hour to develop a color which was measured in the spectrophotometer at 420 nm. The disaccharidase activity in units/ml was estimated from a special formula.

Hydrogen Breath Test

The amount of exhaled hydrogen was measured using the exhaled hydrogen monitor. A sample of the end expiratory alveolar air was obtained from the fasting patient and at 30, 60, 120, 180, and 240 minutes after taking 50 gms of lactose. The samples were injected into the monitor and the hydrogen concentration was expressed as ppm. Lactose malabsorption was diagnosed if the hydrogen concentration in the expired air was more than 20 ppm [15].

The results were analyzed and Z test was used to compare the proportions [16].

$$Z = P_1 - P_2 / \sqrt{Pq\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

Where P represents the proportion, q is 1-p and n represents the number of patients.

Results

The mean age in the three groups ± S.D. was 24.9± 6.6, 32.1 ± 6.0, 33.4 ± 13.2, respectively. Group I was composed of 27 males and 3 females; Group II, 23 males and 7 females; and Group III; 38 males and 22 females.

Oral Lactose Tolerance Test

There was an increase in the blood glucose of less than 20 mg/dl (intolerance) in 11 (36.7%) and 12 (40%) patients in Groups I and II compared to 14 (23.3%) of the control group, but no difference was detected between Groups I and II. Abdominal symptoms in the form of distention, meteorism, colic, flatus, borborygmi and diarrhea were more prominent in Group II compared to Groups I and III ($Z > 1.96$, > 2.58, respectively).

On phenotyping of lactose intolerance into none, mild, moderate, and severe according to the score, moderate and severe intolerance were more evident in the hepatointestinal schistosomiasis group (Table 1).

There was a highly significant decreased inci-

TABLE 1. *Statistical results of lactose phenotyping after 50 gm oral lactose.*

			Lactose Phenotyping			
			Tolerant		Intolerant	
Group	Results	Total	None	Mild	Moderate	Severe
I	No.	30	20	5	3	2
	(%)	100	66.7	16.6	10	6.7
I vs III	Z value	–	> 1.96	< 1.96	> 1.96	< 1.96
I vs II	Z value	–	> 2.58	< 1.96	> 1.96	> 1.96
II	No.	30	9	8	8	5
	(%)	100	30	26.7	26.7	16.6
II vs III	Z value	–	> 2.58	> 1.96	> 2.58	> 1.96
III	No.	60	46	10	3	1
(control)	(%)	100	76.6	16.7	5	1.7

$Z < 1.96$ = non-significant; $Z > 1.96$ = significant; $Z > 2.58$ = highly significant.
Score: 0–2 = mild intolerance; 3–4 moderate intolerance, 5–12 severe intolerance.

TABLE 2. *Scoring system for lactose intolerance by its components in the studied groups.*

		Diarrhea		Abd. gas		Abd. bloating		Abd. cramps	
Group	Score	F	F × S	F	F × S	F	F × S	F	F × S
I	0	27	0	20	0	23	0	26	0
	1	2	1 × 2	5	5 × 1	4	4 × 1	2	2 × 1
	2	1	2 × 1	3	3 × 2	2	2 × 2	1	1 × 2
	3	–	–	2	2 × 3	1	1 × 3	1	1 × 3
Total		30	4	30	17	30	11	30	7
Mean ± SD		0.13 ± 0.4		0.6 ± 0.9		0.4 ± 0.8		0.2 ± 0.7	
II	0	24	0	9	0	14	0	19	0
	1	2	2 × 1	8	8 × 1	6	6 × 1	5	5 × 1
	2	2	2 × 2	9	9 × 2	7	7 × 2	4	4 × 2
	3	2	2 × 3	4	4 × 3	3	3 × 3	2	2 × 3
Total		30	12	30	38	30	29	30	19
Mean ± SD		0.4 ± 0.48		1.27 ± 1.04		0.96 ± 0.92		0.63 ± 0.75	
III	0	55	0	46	0	51	0	53	0
	1	3	3 × 1	8	8 × 1	4	4 × 1	4	4 × 1
	2	2	2 × 2	4	4 × 2	3	3 × 2	2	2 × 2
	3	–	–	2	2 × 3	2	2 × 3	1	1 × 3
Total		60	7	60	22	60	16	60	11
Mean ± SD		0.12 ± 0.41		0.36 ± 0.75		0.27 ± 0.7		0.18 ± 0.56	

F = number of cases (frequency); S = score; F × S = frequency × score; *P* value for I vs. III > 0.05, and for II vs. III < 0.05.

dence of lactose tolerant and increased incidence of lactose intolerant cases in Group II while there was only a significant decreased incidence of lactose tolerant phenotyping in Group I compared to the control group. A significant increase in moderate and severe lactose intolerance was noted in Group II.

There was a mild grade of lactose intolerance in Group I and moderate grade in Group II when the scoring system for diarrhea, abdominal gas, bloating and cramps was used (Table 2).

Studying the pH of stools, the percentage of patients with acidic (pH < 6) stools after oral lactose was greater in Groups I and II, compared to the control group.

Stool osmolarity was greater than 30 in 40%, 46.7%, and 28.3% in Groups I, II, and III, respectively. Statistical analysis showed an increased incidence of stool osmolarity in Groups I and II compared to Group III, while no statistical difference was noted between Groups I and II (data not shown).

The mean lactase activity (LA) in small intestinal biopsies in Group I was not statistically different from Group III, while a significant decrease in Group II was observed. Considering the patients as subgroups, the mean LA of lactose intolerant patients in Groups I and II was lower compared to the control group (Table 3).

TABLE 3. *Lactase activity in jejunal biopsy among the study groups.*

Group		Lactase activity (micromol/gm wet wt./min)		
		Total	Lactose tolerant >1	Lactose intolerant <1
I	Range	0.2–2.88	1.1–2.88	0.2–0.9
	Mean	1.10	1.81	0.39
	S.D.	0.7	0.5	0.1
	P	>0.05	>0.05	<0.05
II	Range	0.1–2.46	1.08–2.46	0.1–0.5
	Mean	0.85	1.51	0.39
	S.D.	0.6	0.51	0.1
	P	>0.05	>0.05	<0.05
III	Range	0.3–3.9	1.6–3.9	0.13–0.99
	Mean	1.21	1.97	0.44
	S.D.	0.7	0.6	0.1
P value (I vs. II)		<0.05	<0.05	<0.05

S.D. = standard deviation.

Oral Lactose Hydrogen Breath Test (OLHBT)

Considering the lactose intolerant Group (> 20 ppm), the difference between the mean values of fasting breath H_2 and the 4-hour concentration was significant in Groups I and II compared to Group III (Table 4), indicating more hypolactasia in patients with intestinal and hepato-intestinal schistosomiasis.

Sensitivity, Specificity, and Efficiency

The OLBHT was the most sensitive (95.3%), specific (89%), and efficient (90.8%) (Table 5).

Discussion

Malabsorption due to schistosomiasis may be due to the direct effect of oviposition [17] or due to

TABLE 4. *Statistical results of oral lactose hydrogen breath test in the study groups.*

Group		Maximum rise in breath H_2	
		<20 p.p.m (tolerant)	>20 p.p.m. (intolerant)
I	No.	22	8
	%	73.3	26.7
	Z	< 1.96	> 1.96
II	No.	21	9
	%	70	30
	Z	> 1.96	> 1.96
III	No.	49	11
	%	81.7	18.3
I vs. II	Z	< 1.96	< 1.96

TABLE 5. *Sensitivity, specificity, and efficiency of different diagnostic methods used for detection of hypolactosia compared to biochemical assay of lactase activity.*

Test	Mean ± S.D.		
	Sensitivity	Specificity	Efficiency
OLTT	79.9 ± 4	77.2 ± 4.2	77 ± 4.2
Symptoms after lactose	74 ± 4.4	71.5 ± 4.5	78.5 ± 4.2
Stool pH	84.5 ± 3.6	78.9 ± 4.1	81.7 ± 3.9
Stool osmolarity	78.4 ± 4.1	78.7 ± 4.1	79.1 ± 4
OLHBT	95.3 ± 2.1	89 ± 3.1	90.8 ± 2.9

OLTT = oral lactose tolerance test; OLHBT = oral lactose hydrogen breath test; sensitivity = A/A+C × 100; Specificity = D/B+D × 100; efficiency = A+D/A+D+B+C × 100; where — A = true positives; B = false positives; C = false negatives; D = true negatives.

the indirect effect as a reflection of portal hypertension in hepatic fibrosis [18].

Lactose malabsorption due to lactase deficiency or hypolactasia has clinical and nutritional significance because of the symptoms that develop after drinking milk including meteorism, borborygmi, abdominal fullness and diarrhea.

We have studied lactase deficiency in intestinal and hepatointestinal schistosomiasis using different methods and compared these with a control group. No control individuals gave a history of milk intolerance but 23.4% were found to have lactase deficiency. This indicates that intestinal lactase deficiency may be subclinical. This concurs with the results of Sahi [19] and Salam et al [20]. The factors that determine the symptomatology of lactase deficiency are the amount of milk or lactose ingested, the concentration of lactase available for hydrolysis, the speed of gastric emptying, and the type of intestinal flora [21].

A flat lactose tolerance curve was observed in 36.7% of patients with intestinal schistosomiasis and 40% of cases with hepatointestinal schistosomiasis. This was significantly higher than in the control group. This may be due to mucosal structural changes of the small intestine caused by schistosomiasis leading to hypolactasia.

The severity of symptoms varied from patient to patient and this has been also found by other colleagues [19].

The abdominal distention found in the patient groups may be due initially to liquid in the small intestine rather than due to gas in the colon as described by Welsh [22]. The abdominal distention was associated with meteorism, borborygmi, and abdominal colic. These symptoms are not sure diagnostic features of lactose intolerance, as some patients had symptoms but were not intolerant. On the other hand, all patients who were intolerant must have had one or more GI symptoms and this agrees with Hammerli et al [23].

There was an increased incidence of fecal osmolarity in Groups I and II. This may be partly explained by intestinal mucosal changes. The causes in these patients may be due to deposition of schistosoma ova [17], increased unconjugated bile salts due to poor liver function [24], hypoproteinemia [25], or portal hypertension [26].

The mean value of lactase activity was significantly less in Group II. This may be due to more histopathological changes in this group.

This study confirmed the advantages of hydrogen breath test. It is highly sensitive, specific, and efficient as previously reported [16,27,28]. It is practical, reproducible, simple, non-invasive, and safe. Although lactose tolerance test has been used for a long time, it has some disadvantages including inaccuracy and frequent venipuncture.

It is concluded that lactase deficiency is more prevalent among schistosomiasis patients since milk and milk products are widely consumed and are major sources of lactose. Lactase deficiency needs a solution. Symptomatic remission can often be achieved by excluding dairy products. The symptoms of intolerant subjects were reduced when milk was treated by commercial lactase [29].

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IN VITRO ACTIVITY OF EIGHT FLUOROQUINOLONES AGAINST CLINICAL ISOLATES OF *BRUCELLA MELITENSIS*

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بما أن مركبات الفلوروكينولون قد جذبت أهتمامًا واسعًا نظرًا لأدائها المتميز في المعمل وداخل الجسم الحي ، وبالنظر إلى خواص حركتها الدوائية وتناولها عن طريق الفم ونفوذها داخل الخلايا، فقد قمنا بإجراء أختبار لمعرفة حساسية ١٤٦ معزولة سريرية حديثة العهد من جراثيم الحمى المالطية نحو ثمانية من عقاقير الكينولونات/ (٤) وخمسة من العقاقير التقليدية. أشتملت العقاقير التي تم أختبارها على سايبروفلوكساسين ونورفلوكساسين وتيمافلوكساسين وسبارفلوكساسين وفليروكساسين وبيفلوكساسين ولوميفلوكساسين و ٩٦٠ ـ CI وتتراسيكلين وجنتاميسين وستربتومايسين وريفامبيسين ومزيج تريمثوبريم مع سلفاميثوكسازول. كانت جميع المعزولات حساسة لعقاقير الكينولونات الثمانية التي تم أختبارها، حيث كان معدل التركيز التثبيطي الأدنى (MIC - 90) يتراوح بين ١٢ , ٠ مغم / لترو ٢,٠ مغم / لتر تبعًا لنوع العقار. تمت ملاحظة أقل معدل للتركيز التثبيطي الأدنى عند إعطاء عقار CI - 960 وأعلى معدل عند إعطاء عقار تيمافلوكساسين وسبافلوكساسين. ظهرت مقومة معزولة واحدة للسايبروفلوكساسين تطورت لديها المقاومة حين كان المريض يعالج بهذا العقار وشملت المقاومة أفراد المجموعة كلها.

Since fluoroquinolones have generated much interest because of their excellent *in vitro* and *in vivo* activity, their pharmacokinetic properties, oral dosing and intracellular penetration, we tested the susceptibility of 146 recent clinical isolates of Brucella melitensis against eight 4-quinolone drugs and five conventional drugs. The drugs tested included ciprofloxacin, norfloxacin, temafloxacin, sparfloxacin, fleroxacin, pefloxacin, lomefloxacin, CI-960, tetracycline, gentamicin, streptomycin rifampicin and trimethoprim-sulfamethoxazole. All the isolates were susceptible to the eight quinolones tested, with an MIC-90 ranging between 0.12 mg/L to 2.0 mg/L depending on the drug. Lowest MCIs were observed with CI-960 and highest temafloxacin and sparfloxacin. One isolate which had developed resistance to ciprofloxacin while the patient was being treated with this drug exhibited cross-resistance to all the members of the family.

Over the last decade the newer preparations of fluoroquinolones have advanced the field of antimicrobial chemotherapy significantly [1]. These are all derivatives of nalidixic acid and exert their activity through inhibition of DNA synthesis by DNA gyrase. The first breakthrough arrived with the development of norfloxacin, a second generation quinolone, which exhibited enhanced activity as an orally active agent for urinary tract infections. Further developments arrived with ciprofloxacin and later by third generation quinolones such as sparfloxacin, temafloxacin, and CI-960. The trend in the synthesis of newer third generation agents has been to increase the number of fluorine residues, resulting in extended spectrum of activity, better penetration and improved pharmacokinetic properties [2,3]. Intracellular penetration of fluoroquinolones provides an interesting alternative in the treatment of intracellular parasites such as Salmonella and Brucella [4,5]. Since brucellosis is endemic in Saudi Arabia, we tested the *in vitro* activity of eight fluoroquinolones against 146 clinical isolates of B. melitensis.

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Material and Methods

A total of 146 isolates of B. melitensis were used in this study. In order to avoid duplication of strains from the same patient, only one strain for each individual patient was tested. The bacteria were isolated from blood, mitral valve, joint fluid or tissues of patients at King Faisal Specialist Hospital and Research Centre (KFSH&RC) which is a 550-bed tertiary care referral facility in Riyadh. All isolates were identified using conventional techniques and consisted of 94 isolates of biotype 1 and 52 isolates of biotype 3 [6]. Minimum inhibitory concentrations of the fluoroquinolones and other antimicrobials were determined by agar dilution method according to the standard method [7]. The medium used was Mueller Hinton II agar (BBL, Cockeysville, MD, USA) which was supplemented with 5% sheep's blood. The bacterial suspensions were adjusted to contain 10,000,000 CFU/ml and spot inoculated to contain 10,000 CFU/spot onto the agar surface with a multipoint inoculator. All incubations were at 35°C for 48 hours in a CO_2 incubator. Sparfloxacin and CI-960 were obtained from the Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI, USA); temafloxacin from Abbott Laboratories (Abbott Park, IL, USA) and lomefloxacin from Searle (Skokie, IL, USA). All other agents were purchased from commercial sources.

Results

Antibacterial activity of ciprofloxacin, lomefloxacin, perfloxacin, fleroxacin, norfloxacin, CI-960, temafloxacin, sparfloxacin, gentamicin, streptomycin, rifampicin and trimethoprim-sulfamethoxazole against 146 isolates of B. melitensis is shown in Table 1. CI-960 was the most active, inhibiting 10 (7%) isolates at an MIC of 0.06 mg/L and 0.12 μg/ml was inhibitory to 99% of the strains of B. melitensis tested. MIC-90 of these isolates to the other seven fluoroquinolones tested ranged between 0.25–2.0 mg/L.

Since the break point for susceptible organisms is considered < 4.0 mg/L, all the isolates were sensitive to the 8-flouroquinolones tested. Different drugs were found to have varying degrees of effectiveness. Although MIC-90 for most quinolones was < 0.5 mg/L, temafloxacin and sparfloxacin were exceptions, requiring 2 mg/L. One strain was resistant to all fluoroquinolones, with an MIC of > 5.0 mg/L. The parent strain of this organism was susceptible to all the fluoroquinolones with an MIC of 0.06–2.0 mg/L. However, while the patient was on ciprofloxacin therapy, he developed resistance to this drug and cross resistance to all other fluoroquinolones [8]. All the 146 strains, including the fluoroquinolone resistant isolate, were susceptible to the conventional drugs tested, with an MIC range of 0.06–1.0 mg/L. None of the fluoroquinolones exhibited *in vitro* synergy with rifampin, streptomycin, gentamicin, tetracycline or trimethoprim-sulfamethoxazole.

TABLE 1. *In vitro activity of fluoroquinolones and other antimicrobials.*

DRUG	MIC (mg/L)			
	# tested	MIC-50	MIC-90	Range
Ciprofloxacin	146	0.25	0.5	0.06–0.5
Norfloxacin	146	0.25	0.5	0.12–0.5
Temafloxacin	146	2.0	2.0	2.0
Sparfloxacin	146	2.0	2.0	2.0
Fleroxacin	146	0.25	0.5	0.06–0.5
Pefloxacin	146	0.25	0.5	0.06–0.5
Lomefloxacin	146	0.12	0.25	0.12–0.25
CI-960	146	0.12	0.12	0.06–0.25
Tetracycline	146	0.25	0.5	0.06–0.25
Gentamicin	146	0.25	0.25	0.12–0.5
Streptomycin	146	0.5	1.0	0.5 –2.0
Rifampicin	146	0.25	1.0	0.12–1.0
Trimethoprim-sulfamethoxazole	146	0.5	1.0	0.12–1.0

Discussion

Brucellosis, although uncommon in developed countries, remains endemic in many developing countries including Saudi Arabia [9]. In Saudi Arabia it is found in rural areas especially where there is tradition of consuming unpasteurized goat, sheep or camel milk and eating uninspected meat. The disease can be severe, involving several organs including the central nervous system and skeletal system.

The fluoroquinolones, due to their improved intracellular penetration and *in vitro* activity against many resistant organisms, were evaluated for activity against clinical isolates of B. melitensis, an intracellular parasite. Previous studies have shown Brucella spp. to be susceptible to some of the fluoroquinolones [4,13–15]; this investigation was extended to test 8 different fluoroquinolones which are either commercially available or in the various stages of development. The relapse rate with conventional drugs used against B. melitensis has been reported to range between 5–70% [10–12]. Compared to these figures, the fluoroquinolones were found to be extremely effective agents against B. melitensis. With the exception of one isolate, ciprofloxacin, fleroxacin, pefloxacin and norfloxacin were all effective against B. melitensis at a concentration of 0.06 mg/L. It was found that with sparfloxacin and temafloxacin, a higher concentration of 2.0 mg/L was necessary in order for them to be effective. Norfloxacin was also found to be effective (0.12 mg/L), but due to poor absorption, is mainly used for urinary tract infections [13–15]. In a recent study from Riyadh, Al-Orainey et al [18] examined the sensitivity of 106 strains of B. melitensis to ciprofloxacin and five other conventional drugs. The range of MIC for their isolates for ciprofloxacin varied between 0.5–2.0 mg/L as compared to 0.06–0.5 for our strains. They also found that three of their strains were resistant to tetracycline and one to rifampicin. On the other hand, we did not encounter any resistance to conventional drugs among our isolates.

Al-Sibai et al [16] assessed the efficacy of the fluoroquinolone ciprofloxacin as a single agent in the treatment of brucellosis. In a prospective, nonrandomized clinical trial, 16 patients were treated with acute brucellosis, with ciprofloxacin orally. Of the 15 (94%) patients who initially responded to therapy, 11 (73%) had no evidence of relapse after 52 weeks follow-up. One of the isolates developed resistance to ciprofloxacin while the patient was being treated with this drug [8]. We tested this isolate and found it to be resistant to all the fluoroquinolones. It, however, remained susceptible to other conventional drugs such as tetracycline, trimethoprim-sulfamethoxazole, rifampicin and gentamicin.

Conclusion

Although very few studies have been conducted as to the efficacy of fluoroquinolones in the treatment of brucellosis [16,17], the initial results along with the *in vitro* susceptibility, intracellular penetration, oral dosing and the improved pharmacokinetic properties of ciprofloxacin and several third generation fluoroquinolones suggest a potential for their use as therapeutic agents. We concur with Al-Sibai et al [16] that further clinical trials are needed to establish their use as a single agent versus conventional therapy.

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A COMPARATIVE ULTRASOUND AND PLAIN ABDOMINAL X-RAY: EVALUATION OF NON-CLASSICAL CLINICAL CASES OF APPENDICITIS

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أجريت دراسة استطلاعية على مئة وتسعة مرضى يعانون من أعراض غير نمطية لالتهاب الزائدة الدودية باستخدام التصوير القياسي بجهاز الموجات فوق الصوتية وتصوير البطن بالأشعة السينية العادية فأوضحت تفوق التصوير بالموجات فوق الصوتية على التصوير بالأشعة السينية من حيث الحساسية والنوعية والدقة العامة. كانت نسبة القرائن السابقة بالنسبة للموجات الصوتية ٨٩٪، ٩٦٪ و ٩١٪ على التوالي ويقابلها فيما يخص الأشعة السينية على الترتيب النسب التالية ٤٨٪، ٩٣٪ و ٦٧٪.. كانت النسبة السلبية لاستئصال الزائدة تساوي ٧٪، أما فيما يتعلق بالتوصل إلى تشخيص بديل، فقد تفوق التصوير بالأشعة السينية العادية على التصوير بالموجات فوق الصوتية نتيجة لانتشار أمراض الأمعاء وحصاة الحالب وذات الرئة القاعدية وجميعها تظهر أكثر بالتصوير بالأشعة السينية. أما التصوير بالموجات فوق الصوتية فكان أكثر جدوى في كشف مرضيات الحوض عند النساء. من المؤمل أن يتحقق مع تحسن الخبرة بالتصوير واستخدام أجهزة عالية الميز للتصوير بالموجات فوق الصوتية ارتفاع نسبة الحساسية والدقة. لذا نوصي باستخدام جهاز التصوير بالموجات فوق الصوتية كاختيار أولي لتصوير حالات التهاب الزائدة الدودية غير النمطية، إلا أنه في المناطق التي تكثر فيها الأمراض المعوية وحصاة المثانة، فمن الأصوب إجراء التصوير بكل من الموجات فوق الصوتية وتصوير البطن بالأشعة السينية العادية حال كون المريض في قسم التشخيص الإشعاعي.

A prospective study of 109 patients with non-classical symptoms of appendicitis using the standard ultrasound (US) machine and plain abdominal x-rays demonstrated that US was superior to plain x-ray with a sensitivity, specificity and overall accuracy of 89%, 96% and 91%, respectively as compared with plain x-ray with 48%, 93% and 67% respectively. The negative appendectomy rate was 7%. In the alternative diagnosis, plain x-ray was superior to US due to the prevalence of intestinal diseases, ureteric calculi and basal pneumonia which were best shown in plain x-rays. US was, however, most useful in detecting female pelvic pathology. It is hoped that with improved imaging expertise and the application of high resolution US machine a higher sensitivity and accuracy can be achieved. US is therefore recommended as the first line in the imaging of non-classical cases of appendicitis. However, in areas where enteric diseases and urinary calculus are endemic, it is prudent to perform both ultrasound and plain abdominal x-rays while the patient is in the radiodiagnostic department.

Appendicitis is a common surgical emergency worldwide and in children it constitutes the most common cause of acute abdomen requiring surgery. In about 80% of cases the diagnosis is purely clinical [1]. However, after over a century of its first description [2] the diagnosis remains an illusion in a significant percentage. Normal appendectomy of 25% is regarded as the surgical norm in suspected appendicitis [3,4] and even the best results describe removal of normal appendices in 10–15% of suspected cases [5]. In women of childbearing age, pelvic problems simulate appendicitis, leading to an unnecessary appendectomy in 35–46% of cases [4,6,7].

With the advent of good imaging devices, the radiological attitude has changed to a more committed approach. Several parameters are now suggested and used in various centers. These include plain abdominal x-rays, ultrasonography (US), barium enema, radioisotope scan and computed tomography (CT) scan.

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With the advent of high resolution real time ultrasound scanners which allow direct visualization of the inflamed appendix or periappendiceal abscess, sonographic evaluation now has a sensitivity of 75–90%, specificity of 86–100% and an overall accuracy of 87–96% [8,9].

While CT, radioisotope imaging and high resolution US machines are not available in most peripheral hospitals, the standard ultrasound machines and radiographic facilities are readily available. Also, where enteric diseases like typhoid or urinary calculus disease are endemic, the value of plain radiographs of the abdomen cannot be overlooked.

This study was designed to find the value of a combined study of ultrasonography and plain films in the evaluation of cases with subclassical features of appendicitis. The aim was to determine the efficacy of plain x-ray and/or US in detecting appendicitis or alternative diagnosis.

Patients and Methods

A total of 109 patients with subclassical clinical appendicitis reporting at the King Khalid University Teaching Hospital, Riyadh, over a period of 14 months provided the material for this study. Examined by surgeons of at least Senior Registrar status, these are patients with possible appendicitis, but in whom the total clinical features were not classical. However, abdominal pain, largely in the right lower quadrant, was present in all cases. Female patients with amenorrhea or other symptoms suggestive of pregnancy were excluded. There were 64 males and 45 females with an age range of 15–78 years and a mean of 22.5 years.

All patients had abdominal US and plain abdominal radiographs. The plain radiographs and ultrasound were interpreted independently by two radiologists. The reports were, however, relayed to the surgeons. The radiologists had no information regarding whether or not the patients were to have surgery. Surgical and pathological results were subsequently collected for analysis.

Sonographic Equipment and Procedures

The ultrasound examination was done using commercially available Siemen's equipment (Sonoline S1-2). A 5-MHz linear array was used for the right iliac fossa and a 3.5-MHz sector transducer for the pelvis with full bladder. Graded compression was applied to the area of interest through the transducer to improve sound transmission and to identify the area of maximum tenderness for thorough examination. Identification of the iliac crest, psoas muscle, iliac vessels and cecal tip provided the landmark for the location of the appendix. Scanning in both sagittal and transverse planes was done from the cecum to the liver area in order to include retrocecal appendix. In females, the pelvis was examined with a full bladder. When the right iliac fossa was normal, a general abdominal scan was performed.

The examination was considered positive if any of the following occurred in isolation or in combination. Visualization of a non-compressible, aperistaltic appendix larger than 6 mm in diameter is noted in Figure 1 [9]. The "target" appearance in Figure 2 is a transverse view comprising a hypoechoic fluid-distended lumen, a hyperechoic inner ring representing the mucosa and submucosa and an outer hypoechoic ring representing the muscularis externa [9]. An appendiceal mass containing localized fluid collection around the appendix, an appendicolith, or free peritoneal fluid particularly in the pelvis and Morison's pouch, is noted in Figure 3. Normal cases had no masses at the right iliac fossa, minimal or no fluid collection and no localized tenderness.

Plain Abdominal X-ray

The standard erect and supine abdomen x-rays were obtained. The erect view was supplemented by the right side up decubitus view in patients who were unable to stand up.

The following findings detected in isolation or in combination with others were recorded as positive: appendiceal fecalith (Figure 4) [11–13]; the colon cut-off sign [14–16] (Figures 5 and 6) comprising the absence of gas and feces in the right lower quadrant, reflex dilatation of the transverse colon and indentation of the colonic gas at the hepatic flexure; obliteration of pelvic fat planes [14]; right lower quadrant mass; extraluminal gas; acute small bowel obstruction [17,18] (defined as distention of more than three loops of small bowel out of proportion to the caliber of the ascending colon). Plain x-rays were considered negative when none of the above was found or indeterminate if intestinal gas pattern did not fit into any of the above patterns.

Patients who had negative plain x-ray and US findings were investigated further with excretory urogram, barium enema or CT depending on the clinical state. These examinations were also used to confirm certain plain film and US findings such as urinary calculi and cecal mass.

Results

Table 1 shows an analysis of the final diagnosis as well as those detected by US or plain x-ray.

Out of the total of 109 patients, 68 had surgery within 24 hours of the radiological findings. These were all positive on US or plain x-ray or both for appendicitis. Out of these 68 patients, 63 had appendicitis (44 unperforated while 19 were perforated) while five patients (7%) had a negative appendectomy.

Of the 46 patients (five surgical plus 41 non-surgical) who did not have appendicitis, 24 had alternative diagnosis. Table 2 shows the analysis of the alternative diagnosis. In 22 patients, the cause of the pain was not found. These patients were discharged home asymptomatic after a few days of observation. These patients were labeled as cases with pain of unknown origin.

Plain X-ray Result

A total of 33 patients were positive for appendicitis while 76 were negative. Out of the positive cases, three had normal appendices at appendectomy. The radiographic sensitivity was therefore 48%, specificity 93%, positive predictive value of 91% and negative predictive value of 56%. The overall accuracy was 67%. The most common positive findings in plain x-ray were small bowel obstruction, appendicolith (Figure 4) and the "colon cut off" sign (Figures 5 and 6).

US Result

Ultrasound detected appendicitis in 59 cases and was negative in 50 cases. Out of the 59 cases, three had normal appendectomy. The sensitivity was therefore 89%, specificity of 96% positive predictive value of 95% and a negative predictive value of 86%. The overall accuracy was 91%. The most common US findings were free peritoneal fluid in the pelvis and Morison's pouch, an appen-

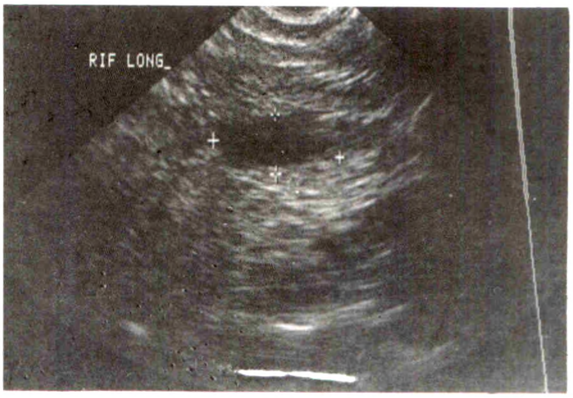


FIGURE 1. Longitudinal scan of the right iliac fossa showing a non-compressible, aperistaltic appendix of 12 mm in diameter. Plain x-ray was normal. Surgery confirmed unperforated appendix.

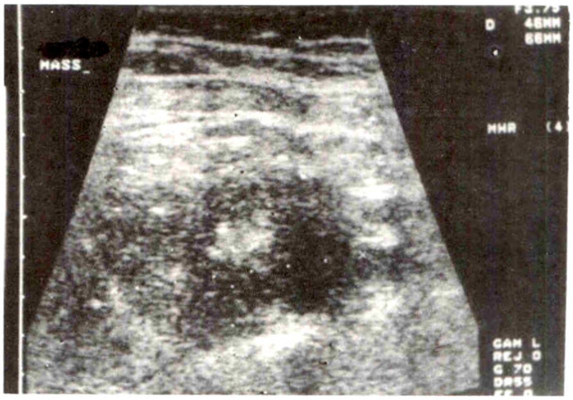


FIGURE 2. Transverse scan of the right iliac fossa showing the "target" sign. The hypoechoic center is only faintly seen. The hyperechoic inner ring representing the mucosa and submucosa and the outer hypoechoic muscularis externa are well seen. Minimal features of small bowel obstruction were seen on plain x-ray. Surgery confirmed unperforated appendix.

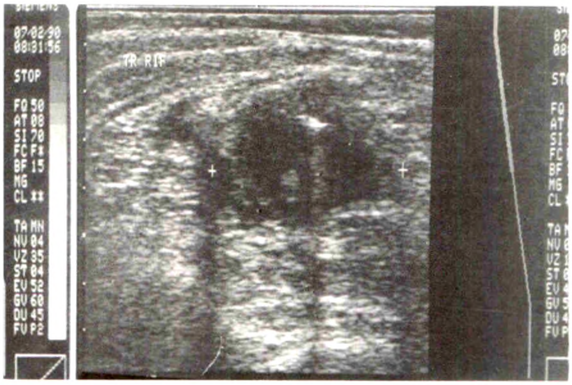


FIGURE 3. Transverse scan of the right iliac fossa showing an appendiceal mass. A mixed density mass with poorly defined boundaries. The hyperechoic area possibly represents gas or mucus. Plain x-ray showed the "colon cut off" sign Figure 6 (same patient). Surgery confirmed perforated appendix.

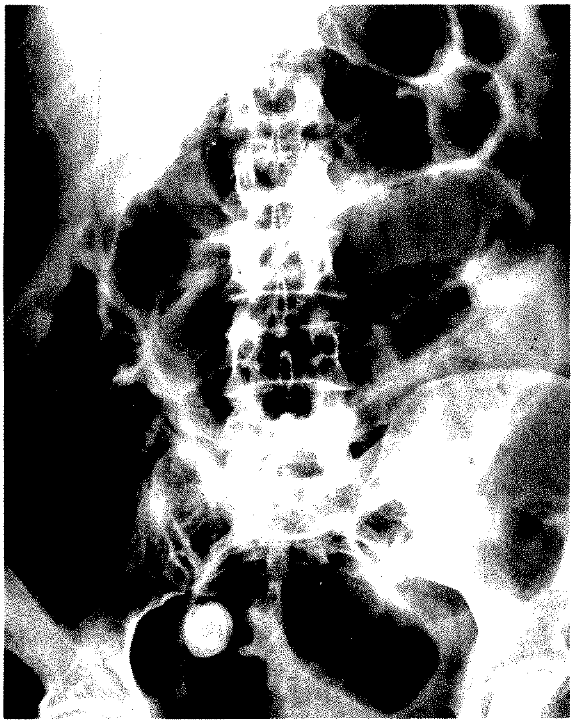
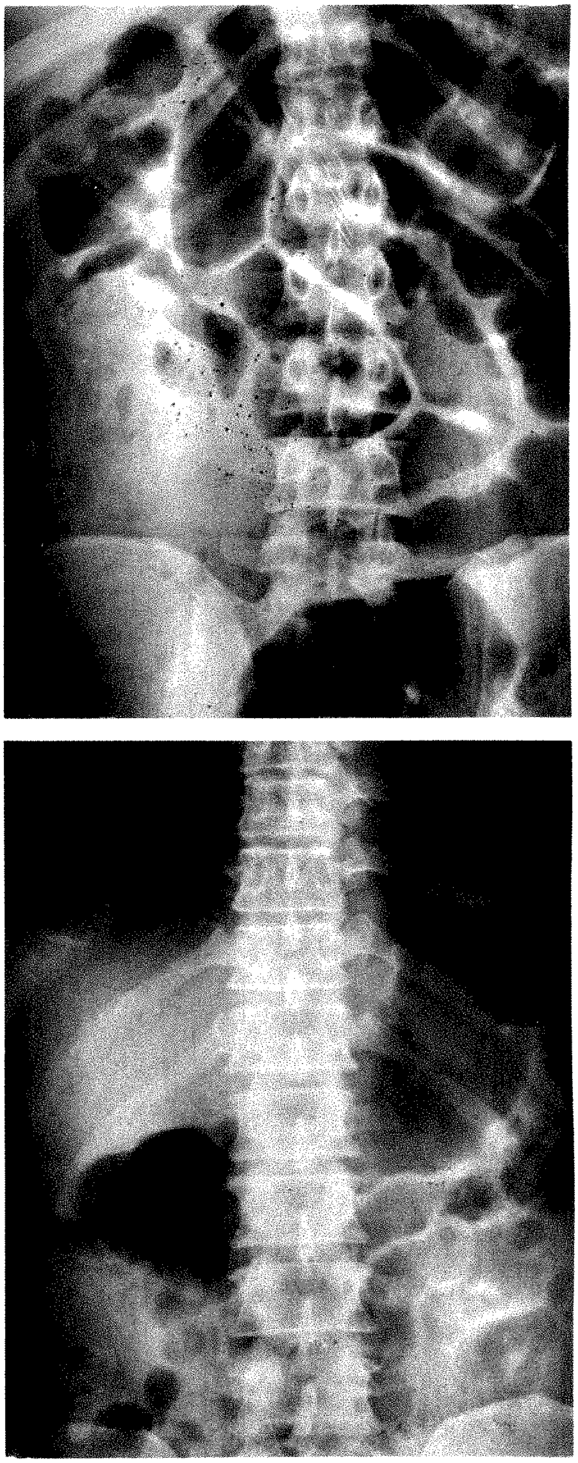


FIGURE 4. A large appendicolith is shown at the RIF. Gas-filled large and small bowel loops are also present. Gallstone ileus was also considered. A perforated appendix with abscess and appendicolith were found at surgery.

dix mass or a thickened bowel loop simulating "target" sign in the appendix area. In the alternative diagnosis, US provided or suggested eight out of the 24 cases, i.e., 33%. Most of these cases were gynecological in origin.

A total of 32 patients were positive for appendicitis in both US and x-ray examinations. All of these were positive for appendicitis at surgery except one who had ileocecal tuberculosis.

Out of the five patients who had negative appendectomy, two were falsely positive in US alone, two in plain x-ray alone and one in both, as earlier mentioned. In the false positive cases, free peritoneal fluid in the pelvis and Morison's pouch were the findings on US while features of small bowel obstruction were the findings on plain x-ray. Three of these cases had urinary tract infection while one had radiolucent ureteric stone, all confirmed by excretory urogram. The false negative cases of appendicitis occurred in largely obese patients with unperforated appendices on the US imaging while those undetected by plain x-ray were both perforated and unperforated.



FIGURES 5 and 6. Two separate patients with plain supine abdominal x-rays showing the "colon cut off" sign. The three components are: relative absence of gas at the right lower quadrant, reflex dilatation of the transverse colon and amputation of the colonic gas at the hepatic flexure. Note associated feature of distended small bowel loops.

A total of 22 patients were negative in all forms of investigation and were therefore labeled as pain of unknown origin.

Discussion

The negative appendectomy rate in this study group of patients with non-classical symptoms of appendicitis was 7%. US was superior to plain x-rays in the detection of appendicitis with a sensitivity, specificity and overall accuracy of 89%, 96% and 91%, respectively as opposed to plain x-ray with 48%, 93% and 67%, respectively. However, in the group with alternative diagnosis, plain x-ray detected more abnormalities, largely due to the nature of the abnormalities such as basal pneumonia, calcified ureteric stones, intestinal diseases with perforation or bowel obstruction. Although US could indirectly suggest the presence of these pathologies, plain x-rays are currently considered superior to US with the exception of pelvic pathologies. Campbell and Gunn [19] emphasized the limited contribution made by plain abdominal x-rays in assessing patients with suspected appendicitis, urinary tract infection and non-specific abdominal pain. On the other hand, the literature is replete with reports of increasingly accurate results using US in the evaluation of cases of appendicitis and various abdominal pathologies. However, US has its limitations, especially as efficiency is dependent on the resolution of the ultrasound machine, the imaging expertise of the operator, as well as obesity and the amount of intestinal gas in the patient.

In appendicitis, the most commonly found abnormalities in plain x-ray were small bowel obstruction followed by appendicolith and the "colon cut off" sign. On US, free peritoneal fluid and a loop of thickened bowel loop simulating the "target" sign in the appendix area and appendiceal mass were the most common findings. Free peritoneal fluid occurred in both perforated and unperforated appendicitis and was also the finding in two of the false positive cases of appendicitis on US. Therefore, as common and useful as this sign may be, it should be interpreted with caution since it can occur in various other abdominal conditions as well as in normally ovulating females. Ileocecal tuberculosis was the cause of the false positive cases on both US and plain x-ray. This is not surprising since bowel wall thickening below the cecum and features of small bowel obstruction can occur in various conditions including enteric tuberculosis, Yersinia enterocolitis and Crohn disease. Urinary tract infection was subsequently found in three (all females) of those who had negative appendectomy. The false negative cases

TABLE 1. *The main final diagnosis and a comparison of numbers detected by US and plain x-ray.*

Final diagnosis	Total number	Number detected by US	Number detected by x-ray
Appendicitis	63	56	30
Alternative diagnosis	24	8	13
Pain of unknown origin	22	–	–
Total	109	64	43

TABLE 2. *Analysis of the alternative diagnosis including US and plain x-ray findings.*

Alternative diagnosis	Total number	US detection	X-ray detection
Urinary calculus	6	1 (renal)	4 (1 renal, 3 ureteric)
Enteritis	5	1 (mesenteric lymph node)	3 (2 with bowel perforation)
Urinary infection	3	—	—
Small bowel obstruction	2	—	2
Mesenteric infarction	2	1 (bowel wall thickening)	2 (1 sickle cell and 1 cardiac pathology)
Ruptured ectopic pregnancy	2	2	1 (pelvic fluid collection)
Twisted ovarian cyst	1	1	—
Pelvic inflammatory disease	1	1	—
Cecal malignancy	1	1	—
Right basal pneumonia	1	—	1
Total	24	8	13

in US were largely due to poor imaging in the initial stage of the study and problems with obesity. Also, these patients had unperforated appendicitis. There is no doubt that a high resolution US machine would give better details. However, two-thirds of the cases of appendicitis were unperforated.

Also significant is the fact that when both US and plain film were positive or negative, the positive and negative predictive values were higher than either US alone or plain film alone. This is because each modality is capable of detecting certain parameters suggestive of appendicitis where the other could not. For example, while x-rays are largely dependent on intestinal bowel gas pattern, the presence of gas is a deterent to adequate US imaging. Therefore, a dual positive result has a maximum probability of appendicitis and a dual negative result is more reassuring. Hence, the 22 patients who were discharged home symptom-free had negative findings on US and plain x-ray as well as on other investigations that were carried out.

Although computed tomography (CT) evaluation is not mentioned in our study, Balthazer et al [20] have used CT successfully to diagnose appendicitis in patients with ambiguous clinical findings. However, CT is particularly useful in characterizing inflammatory masses around the appendix [21]. The distinction between periappendiceal phlegmon and abscesses is important since the former is often managed conservatively with antibiotics while the latter can be drained percutaneously with CT guidance when it is well defined [8]. The authors also used CT to show the extent of periappendiceal masses or collections whenever the patients presented with palpable masses. High risk patients such as hemophiliacs and patients with heart failure have also been investigated with CT following negative US and plain x-ray studies. In these instances the CT was normal.

In conclusion, an accurate surgical evaluation remains the mainstay of diagnosis of appendicitis. However, when the presentation is atypical, radiological evaluation using US is suggested as the first line of evaluation. If ultrasound is inconclusive or negative, plain radiographs should be obtained for evaluation before the patient leaves the department. In areas where the quality of US imaging is sub-optimal and where enteric diseases such as typhoid and urinary calculi are endemic, it is prudent to use both US and plain abdominal x-ray as a preliminary assessment.

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SPINAL TUMORS: EXPERIENCE AT KING KHALID UNIVERSITY HOSPITAL

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يتناول هذا المقال البيانات ذات العلاقة بثلاثين حالة متابعة من أورام القناة الشوكية تم علاجها في مستشفى الملك خالد الجامعي في الفترة بين عام ١٩٨٤ و ١٩٩١م. كانت نسبة الذكور إلى الإناث ٢,٧٥ : ١. وكانت أعمار ما نسبته ٣٠٪ من الحالات دون العشرين عامًا. بينما تجاوزت أعمار ما نسبته ١٧٪ من الحالات الستين عامًا. كانت نسبة أورام الدماغ إلى أورام القناة الشوكية في وحدتنا تعادل ١٢,٣ : ١. ونسبة ورم شوان إلى الورم السحائي ١,٦ : ١. كانت السرطانة الإنتقالية مسؤولة عما نسبته ١٣٪ من الحالات فقط، توضعت ٣٥٪ من الأورام في العمود الصدري. كانت نسبة أورام الحبل الشوكي ١٧٪ من مجموع الحالات. تحسنت نسبة ٦٣٪ من الحالات عقب العملية الجراحية على وجه الإجمال بينما ظلت حالة ما نسبته ٣٧٪ دون تغيير.

This paper summarizes data on 30 consecutive spinal tumors treated at King Khalid University Hospital (KKUH) between 1984–1991. The male:female ratio was 2.75:1. Thirty percent of cases were less than 20 years of age while 17% were more than 60 years of age. The brain to spinal cord tumor ratio in our unit was 12.3:1. The ratio of Schwannoma to meningioma was 1.6:1. Metastatic carcinoma accounted for a mere 13% of cases and only 35% of tumors were located in the thoracic spine. Intramedullary tumors accounted for 17% of cases. An overall 63% of cases improved postoperatively while 37% remained unchanged.

Spinal tumors are a fairly common pathology accounting for 2% of all tumors [1], and 8–20% of central nervous system (CNS) tumors [2–7]. Surgery for spinal tumors is older than 100 years [8] and the literature is rich with statistical reviews reporting large series of spinal tumors [1–3,9–11]. Information about the incidence and patterns of spinal tumors in Saudi Arabia or the Middle East, however, remains insufficient. This article provides a survey involving 30 cases of spinal tumors that were treated during a seven-year period in a neurosurgical unit in Riyadh, Saudi Arabia. It is appreciated that the number of cases is modest; nevertheless, the material presented is a first attempt at providing data regarding characteristics associated with spinal tumors in Saudi Arabia.

Methods

This is a retrospective analysis of 30 consecutive cases consisting of spinal tumors that were managed at King Khalid University Hospital (KKUH), between 1984–1991. The study included all tumors causing damage to the spinal cord, cauda equina, and spinal nerve roots. Each case was analyzed by using hospital records and the following data were collected: age, sex, clinical presentation, preoperative Nurick Grade [12], histological diagnosis, radiological findings, level of the lesion, extent of surgical treatment and other treatment modalities, duration of hospital stay and the Nurick Grade at follow-up.

Results

There were 22 males and 8 females with an age range of 1–70 years (mean 33.2 years). The distribution of cases according to the histology of

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tumor, age and sex is noted in Table 1. The clinical features of the cases at presentation appear in Table 2. The metastatic carcinomas were prostatic in origin in two cases, colonic in one case and nasopharyngeal in one case. Ten (33%) cases were investigated using myelography alone while 19 (63%) cases had myelography with computed tomographic (CT) scans and one case (3%) had a magnetic resonance imaging (MRI) scan. The spinal levels affected by the various tumors are noted in Table 3. Surgery was performed using a posterior approach on all surgical cases. Excision was considered complete in all Schwannoma cases, four (80%) of the meningioma cases, one (20%) of the intramedullary tumors in addition to the case with dermoid. Postoperative radiotherapy was administered in all cases involving metastatic carcinoma, myeloma, sarcoma, neuroblastoma and lymphoma. In addition, the cases with prostatic carcinoma metastasis received hormonal therapy and cases with lymphoma, sarcoma and neuroblastoma received chemotherapy. The duration of hospital stay ranged between 11 to 130 days (median 31 days). One patient with Schwannoma developed malignant recurrence of the tumor three years after initial diagnosis and expired one year later. Another patient with metastatic disease presented with total paraplegia for more than one week. This was the only case in the series that did not have surgery. The patient died from a pulmonary embolus one month following presentation. One patient with myeloma died from systemic disease ten months postoperatively. Of the five cases with intramedullary tumor, one with a lumbar ependymoma had a total excision and remains well at two years' follow-up. The remaining four cases presented with major neurological deficits (Nurick Grades 4

TABLE 1. *The distribution of cases in the series according to site, histology, sex and age.*

Site No. (%)	Histology	Sex		Age				Total no. (%)
		Male	Female	<20	20–40	41–60	>60	
Extradural	Metastatic carcinoma	4	0	0	1	1	2	4 (13%)
9 (30%)	Myeloma	2	0	0	0	2	0	2 (7%)
	Ewing sarcoma	2	0	2	0	0	0	2 (7%)
	Neuroblastoma	1	0	1	0	0	0	1 (3%)
Intradural	Schwannoma	5	3	1	5	2	0	8 (27%)
Extramedullary	Meningioma	1	4	0	2	1	2	5 (17%)
16 (52%)	Lymphoma	0	1	0	0	0	1	1 (3%)
	Paraganglioma	1	0	0	1	0	0	1 (3%)
	Dermoid	1	0	1	0	0	0	1 (3%)
Intramedullary	Astrocytoma	3	0	3	0	0	0	3 (10%)
5 (17%)	Ependymoma	2	0	1	1	0	0	2 (7%)

TABLE 2. *Clinical features of cases in the series on admission.*

	Clinical feature No. (%)			
Tumors	Pain	Motor disturbance	Sensory disturbance	Sphincter disturbance
Schwannoma	5 (63%)	7 (86%)	5 (63%)	3 (38%)
Meningioma	2 (40%)	4 (80%)	2 (40%)	1 (20%)
Metastatic carcinoma	4 (100%)	4 (100%)	5 (100%)	4 (100%)
Intramedullary tumor	2 (40%)	5 (100%)	5 (100%)	3 (60%)
Others	6 (75%)	6 (75%)	4 (50%)	4 (50%)
Total	19 (63%)	26 (87%)	21 (67%)	15 (50%)
Mean duration of symptoms (months)	10	8.4	75	0.5

and 5) and had partial excisions. Although these patients did not deteriorate postoperatively, three remained disabled at follow-up between three to six months while one patient who also had a concomitant malignant glioma in the brain died at four months. Figure 1 shows the changes in the Nurick grading for all cases prior to and following treatment at the time of discharge from the hospital. Follow-up ranged between 2 to 60 months (mean 14.4 months). Unfortunately, ten (33%) cases had a follow-up of less than one year.

Discussion

The incidence of spinal tumors in the West ranges between 1.1 to 12.9/100,000 population [4,5]. The incidence in our unit was 4.3 cases/year. It is difficult to accurately estimate the population served by our hospital. However, by comparison with our hospital's incidence of amyotrophic lateral sclerosis (ALS) of 2.5 cases/year [13], it appears that spinal tumor is 1.72 times more common than ALS in our hospital. Using the assumption that ALS has a worldwide prevalence of 5/100,000 it appears that spinal tumor in Riyadh has a prevalence of 8.5/100,000. Information regarding the incidence of spinal tumors in Saudi Arabia cannot be calculated using the available data. Since we have treated 368 brain tumors during the same seven-year period, our ratio of brain to spinal tumor was 12.3:1.

Our overall male:female ratio was 2.75:1 which is higher than the ratio reported in other recent studies [1,2]. Not surprisingly, meningioma was more common in females (ratio 4:1) and excluding isolated cases of various tumors in the series, meningioma was the only tumor that had a higher incidence in females than in males which has been noted [1,2,14]. In this series, Schwannoma had a male:female ratio of 1.6:1 while all four patients with metastatic carcinoma and five patients with intramedullary tumor were male. Thirty percent of our cases were aged less than 20 years while 17% were older than 60. Out of the nine patients younger than 20, four (44%) had intramedullary tumor, two (22%) Ewing sarcoma, one (11%) neuroblastoma, one (11%) dermoid, and one (11%) Schwannoma. Children accounted for 6.8–19% of cases conducted in recent studies [1,2]. It

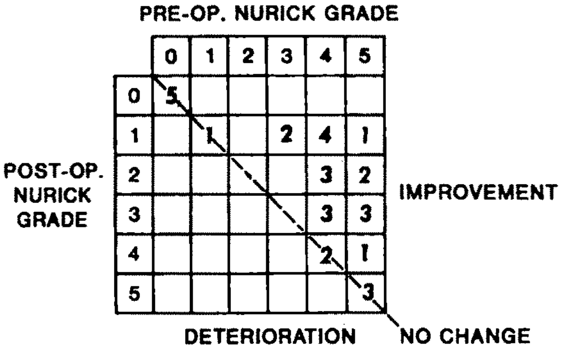

FIGURE 1. Diagram shows the changes in Nurick Grade before and after treatment for all cases. Grade O: root signs only; Grade 1: cord signs, no difficulty walking; Grade 2: difficulty walking, able to work; Grade 3: difficulty walking and working; Grade 4: walks with support; Grade 5: bedridden.

TABLE 3. *The spinal levels involved in cases in the series.*

Tumor	Number of cases by site				
	Cervical	Thoracic	Lumbosacral	Multiple	Total
Schwannoma	2	3	4	–	9*
Meningioma	2	1	2	–	5
Metastatic carcinoma	0	4	–	–	4
Intramedullary tumors	1	1	1	2	5
Myeloma	–	2	–	–	2
Sarcoma	–	–	1	1	2
Lymphoma	–	–	1	–	1
Neuroblastoma	–	–	–	1	1
Paraganglioma	–	–	1	–	1
Dermoid	–	–	1	–	1
Total	5 (16%)	11 (35%)	11 (35%)	4 (13%)	31 (100%)

* One case had 2 Schwannomas.

has been noted that children have a high incidence of desembryonoblastic tumors which may increase to 55% [2] while intramedullary gliomas, also common in children, account for 25–32% of cases [2,15]. Seventeen percent of our patients were older than 60 and of the five patients in this age group, two (40%) had metastatic carcinomas, two (40%) meningiomas, and one (20%) lymphoma. The high incidence of metastatic tumors among the elderly is not unusual [1,2,10].

Table 4 summarizes the incidence of various tumors found in our series and in reported studies [1–3,9,11]. The ratio of Schwannoma to meningioma found in our series was 1.6:1. Intramedullary glioma accounted for 17% of our cases. Sixty percent of these cases had astrocytoma while 40% had an ependymoma. There were no cases of glioblastoma or oligodenroglioma. In the series reported by Cheng [2], there were more astrocytomas than ependymomas. However, other reports [1,9] state the opposite. In this series, metastatic carcinoma was diagnosed in 13% of cases. A recent report from Germany [1] states that 43% of spinal tumors in the West, to date, are due to metastasis. The possible underestimation of metastatic tumors in our series may be the result of selection bias. It is more than likely that a significant number of these patients are presently being treated at local hospitals or present in poor clinical condition, rendering them unsuitable for transfer to a central neurosurgical unit. Our patients had primary malignancy from the prostate, colon and nasopharynx. Wenker and Reuter [1] reported 1,314 metastatic spinal tumors and found that the primary site of malignancy originated from the bronchus (15%), breast (12%), prostate (9%), and kidney (8%). It is interesting to note that we did not encounter any cases of spinal metastasis from a bronchial carcinoma. This may be due to the fact that lung cancer in Saudi Arabia accounts for only 6% of all cancers [16]. Prostatic cancer in Saudi Arabia accounts for only 3% of all cancers [16], but because this is usually associated with a longer survival rate than bronchial cancer, we are likely to encounter more prostatic spinal metastasis than bronchial.

Pain was an important feature at presentation in 63% of cases. The lowest incidence of pain found in meningiomas and intramedullary tumors was 40%. Motor disturbances occurred in 87% of cases, sensory disturbances (67%) and sphincteric disturbances in 50% of cases. Patients with Schwannoma and meningioma suffered a greater number of motor disturbances than pain which is not unusual [1,2]. In patients with metastatic carcinoma, pain was a main symptom at presentation and was as common as motor, sensory and sphincteric disturbance.

Tumors were located in the cervical spine in 16% of cases, which concurs with other reports [1,2]. However, only 35% of our cases had tumors in the thoracic spine which is lower than the 51-59% stated in recent studies for spinal tumors located in the thoracic spine [1,2]. The reason for the relatively low incidence of thoracic spinal tumors is the low incidence of metastatic tumors (17%) frequently found in the thoracic spine [1,17]. Early in the series, our cases were investigated by myelography alone but more recently, myelography performed with CT scans have been the standard investigation. Unfortunately, MRI is not available in our hospital. It has now been rec-

TABLE 4. *Comparison of our data with previous reports.*

Author	Jamjoom	Wenker(1)	Cheng(2)	Nittner(3)	Sloof(9)	Izumida(11)
Number of cases	30	3048	1639	4885	1322	729
Year	1992	1986	1982	1976	1964	1967
Percentage of cases						
Schwannoma	27	13	46.8	23.1	29	44.9
Meningioma	17	19	12.4	22.4	25.5	11.4
Intramedullary tumor	17	6.8	10	15.7	19.3	8.3
Metastatic carcinoma	13	43	5.5	6	?	4.4
Vascular	0	?	6.0	6.5	6.2	6.2
Sarcoma	7	1.6	4.4	8.2	11.9	6.7
Others	20	16.5	14.9	26.3	8.1	18.1

ognized that MRI remains the optimal investigation for spinal cord tumors [18].

Total surgical excision was technically impossible for one case with meningioma and the case with paraganglioma [19]. To date, both patients remain neurologically stable at 12 and 24 months follow-up, respectively. The difficulty in performing total excision of intramedullary tumor is well documented [20,21]. Three cases with metastatic carcinoma had decompressive laminectomy with good postoperative recovery while surgery was not performed in one patient who had been rendered paraplegic for one week and had multiple spinal bony metastasis. The issue of patient selection for surgery for metastatic disease of the spine has been controversial, but is now being recognized that patients with complete physiological transection of the spinal cord and rapid neurological deterioration and metastatic disease of the spine at more than one level are unlikely to benefit from surgical intervention [22].

Overall, 19 (63%) patients improved following surgery, 11 (27%) remained unchanged while no cases of postoperative deterioration were reported (Figure 1). We are aware of four (13%) patients who died between one month to four years following the diagnosis of spinal tumor. Unfortunately, early in the study some of our patients were lost to follow-up. This was because a significant number of patients were referred from outside Riyadh and had postoperative radiotherapy elsewhere. Therefore, since 33% of cases had follow-up less than one year and due to the small number of cases in different tumor groups, extensive data about the long-term outcome of cases of spinal tumors in the series could not be provided. However, the primary goal of this study was to provide data on the nature, relative frequency, location, age and sex distribution of spinal tumors in Saudi Arabia.

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EPIDEMIOLOGICAL STUDY OF PATIENTS WITH ACUTE ASTHMA ATTENDING ACCIDENT AND EMERGENCY DEPARTMENT

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أجريت دراسة على نوبات الربو لدى المرضى الذين راجعوا قسم الطوارىء في مستشفى الملك عبدالعزيز الجامعي وذلك خلال الفترة من شهر أغسطس ١٩٨٩م إلى شهر يوليو ١٩٩٠م. كان اجمالي عدد الحالات التي راجعت قسم الطوارىء خلال تلك الفترة ٨٩١٧٨ حالة منها ٥١٠١ حالة ربو. قدرت نسبة أنتشار الربو حسابيًا على أنها ٥,٧٢٪ نسبة إلى جميع الحالات المرضية الأخرى التي راجعت قسم الطوارىء في تلك الفترة. ووجد أن الإصابة بالربو أكثر حدوثًا لدى الصبيان. راجع معظم المصابين بنوبة ربو حادة قسم الطوارىء في أواخر النهار وفي الليل. ازدادت معاودة نوبات الربو بالتناسب مع العمر وكانت شدة الإصابة لدى الذكور أكثر منها لدى الاناث. لاحظنا وجود نزعة موسمية هامة إذ بلغت الإصابة بالربو ذروتها في شهري ديسمبر ومايو. كانت نسبة قبول المصابين بنوبة حادة من الربو في المستشفى ١,٥٪ تقريبًا من جميع نوبات الربو. لم تحدث وفيات أثناء فترة الدراسة.

A study of episodes of asthma was conducted in patients attending the Accident and Emergency (A&E) Department of King Abdulaziz University Hospital (KAUH) from August 1989 to July 1990. The total number of cases reporting to the A&E Department during this period was 89,178; of which 5,101 presented with episodes of asthma. The estimated prevalence of asthma was calculated to be 5.72% in relation to all other diseases reported to the A&E Department during this period; asthma was found more frequently among boys. A majority of patients with acute asthma attended the A&E Department during late afternoon and at night. Repeated episodes of asthma increased proportionately with age, and were more severe in males compared to females. A significant seasonal trend was noted, with two peaks noted during December and May. Hospital admissions for patients experiencing acute asthma was approximately 1.5% of all reported asthma episodes. No deaths were reported during the study period.

Bronchial asthma, one of the most common chronic lung disorders, is widely recognized as a significant cause of illness and disability [1,2]. Although medical treatment has improved significantly and the delivery systems for the medication have become more sophisticated, the morbidity associated with asthma has increased considerably over the past two decades [3].

Nocturnal bronchoconstriction with an early morning decrease in peak expiratory flow (PEF) is common in asthma [4–6], however, the mechanism is poorly understood [7,8]. There is also evidence that most deaths due to asthma occur at night [7,9,10]. Among factors which increase the risk of death during an acute attack of asthma are previous life-threatening attacks; asthma which is not properly controlled, even in those with a normally mild illness, may be fatal [11]. This study demonstrates the epidemiological determinants of acute asthma among patients attending the Accident and Emergency (A&E) Department of King Abdulaziz University Hospital (KAUH).

Subjects and Methods

King Abdulaziz University Hospital (KAUH) is a teaching hospital with 270 beds, serving a multiracial population of mixed socioeconomic status.

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The study population comprised all patients who were treated for acute asthma in the Accident and Emergency (A&E) Department of KAUH between August 1, 1989 and July 31, 1990. The patients were treated by general practitioners, internists and pediatric residents under the supervision of staff physicians. Consecutive emergency room records were reviewed over a 12-month period by members of the asthma follow-up clinic at KAUH. Data documented in the case records by the nursing and medical staff for all visits to the emergency room were reviewed and separated into four categories: (1) patient details: age, sex, date, time of attendance, presenting symptoms, precipitating factors and past history of asthma; (2) physician assessment in the A&E Department: observations and measurements recorded and investigations performed; (3) treatment prior to arrival in the A&E Department, while in the A&E Department, and upon discharge; and (4) clinical outcome: admitted, discharged or expired. The major inclusion criterion was the diagnosis of asthma. Patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), pneumonia, cardiac failure, or trauma; infants with acute bronchiolitis and children with pulmonary or cardiac disorders were excluded from the study.

Analysis of the data was conducted by using an IBM compatible computer and Systat statistical package [12]. Standard statistical procedures such as chi-square and Z-test were used in the analysis of the data [13]. The results throughout the study were considered significant whenever the P value was < 0.05.

Results

A total of 4,325 patients with asthma visited the A&E Department 5,101 times during the 12-month study period. These visits represent 5.72% of the total visits (89,178) by all categories of patients to the A&E Department during the same period (Figure 1). The frequency of visits increased progressively from 521 (10.2%) in October to 639 (12.5%) in December. During the 12-month study period, a significant seasonal trend was noted, with an increase in the frequency of attendance in December and May. The frequency of attendance to the A&E Department was at its highest level in the age group 45 years and older, and at its lowest for those between 15–24 years. The average number of visits per person was 1.43 and 1.03, respectively during the study period (Table 1).

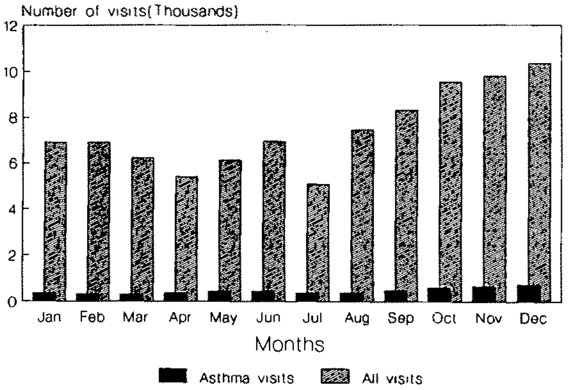

FIGURE 1. Distribution of all visits and asthma visits to A&E Department, KAUH.

TABLE 1. *Distribution of patients with asthma by age and frequency of attendance in the A&E Department, KAUH, 1989.*

Age (yr)	No. of patients with asthma		Frequency of attendance		Average attendance
	No.	%	No.	%	per person
<5	890	20.58	969	19.00	1.09
5–14	787	18.20	867	17.00	1.10
15–24	475	10.98	489	9.59	1.03
25–44	1124	25.99	1275	24.99	1.13
45+	1049	24.25	1501	29.42	1.43
Total	4325	100.00	5101	100.00	1.18

Male patients with asthma (58.54%) attended more frequently in the A&E Department, compared with females (41.46%). Male patients with asthma younger than age 15 and older than age 45 attended the A&E Department more frequently as compared to females (Z = 6.44, 7.21 and 1.99, respectively), whereas female patients with asthma, age ranging from 15–44 years, attended the A&E Department more frequently as compared to males (Z = 3.27, 11.99, respectively). These differences were statistically significant, where $P < 0.05$.

The majority of children younger than five years (57.67%) and ages 5 to 14 years (54.74%), visited the A&E Department during the night (1800 hours to 0600 hours), as compared with other age groups. Patients with asthma over 45 years of age

(37.01%), visited the A&E Department during the daytime (0600 hours to 1200 hours), as compared with other age groups (Figure 2). A greater proportion of patients with asthma age 15 to 24 years (32.71%) visited the A&E Department during the afternoon (1200 hours and 1800 hours), as compared to other age groups. These differences were statistically significant where the chi-square was 89.81 ($P < 0.001$).

Among patients with asthma attending the A&E Department during the early morning hours (0100 hours to 0600 hours), males outnumbered females more significantly ($Z = 3.66$, $P < 0.001$); whereas a significantly larger number of female patients with asthma presented during the afternoon hours (1300 hours to 1800 hours) where $Z = 3.72$, $P < 0.001$ (Figure 3).

The seasonal variation demonstrated that children under the age of 15 years visited the A&E Department more frequently during the winter months than summer months. Whereas patients with asthma over 25 years of age attended the A&E Department more frequently during the summer months as compared to winter months, $P < 0.001$ (Figure 1).

There were no deaths reported during the study period due to asthma; hospital admission was required in approximately 15% of the visits.

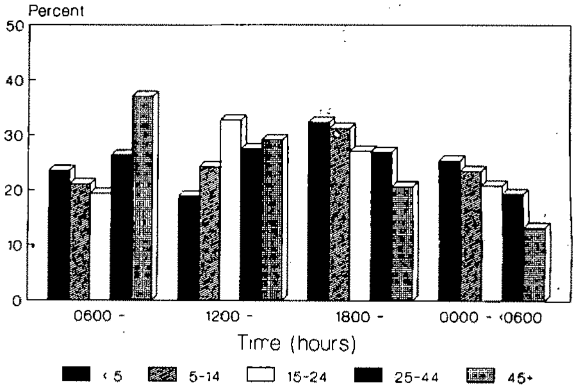

FIGURE 2. Distribution of asthma visits to A&E department by age and time of attendance, KAUH.

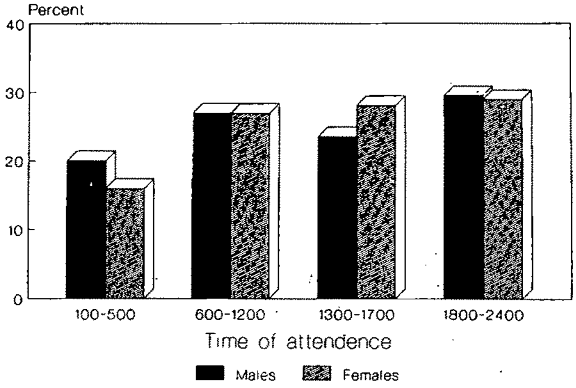

FIGURE 3. Distribution of asthma visits to A&E Department by sex and time of attendance, KAUH.

Discussion

Of the patients with whom details were recorded, only 7.7% had no previous history of asthma and the majority of patients (70.6%) were younger than 45 years with the diagnosis of asthma being reasonably accurate in this age group. Also, the exclusion of patients with acute exacerbation of COPD, patients with complicating diseases and infants with acute bronchiolitis minimized the probability of entering non-asthmatic cases in the present study.

In KAUH, as in many medium-size general hospitals, acute asthma is a fairly common cause of attendance in an A&E Department. The present study revealed that the estimated prevalence of asthma in the patient population attending the A&E Department was 5.72%. In previous studies, the estimated prevalence of asthma within the practice population varied from 1.8% to 6.7% [14,15]. It was reported that such discrepancy was due to the various methods of case findings used in the studies [16,17].

In this study there was a significant seasonal variation with episodes being more common during late fall and early winter. This observation is consistent with the literature reporting seasonal trends in patients hospitalized with acute asthma [22]. However, when the patients were classified according to age, winter months became a peak period for children younger than 5 years of age, and late spring and summer months became a peak period for adults and older patients. These patterns may be explained by the role of respiratory infections and environmental allergens as triggering agents for severe attacks [16].

It has been reported that there is a positive relationship between repeated attendance at the A&E Department and severity of disease due to acute attacks [11,17,18]. This study found that increased age was associated with frequent attendance in the A&E Department. Almost twice as many boys as girls attended during the study period; a finding that tends to confirm the greater frequency of occurrences of asthma in boys. Similar gender differences were reported in other studies [19,22]. A greater proportion of male patients with asthma in the 45 year age group attended the A&E Department frequently during the study period; this may explain the male to female ratio of 1.55:1.

Deaths due to respiratory disease is more common at night, which has been well documented in patients with asthma [20]. In a published series, 93 out of 219 deaths occurred between midnight and 0800 hours [21]. In this study, young children and adult women attended the A&E Department mainly in the evening and late afternoon hours. This may reflect the circadian variation in airflow obstruction. It may also be due to work schedule of the head of the family and/or inavailability of primary physician treating such patients at night.

This study provides preliminary data on patients with asthma reporting to the A&E Department. It is anticipated that similar attempts will be made by other health care service providers in Saudi Arabia to implement a reporting system for bronchial asthma. This may encourage concerned health care personnel to develop preventive measures, health education, and intensive support services for patients with asthma nationwide.

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ACUTE RHEUMATIC FEVER IN KUWAIT: THE DECLINING INCIDENCE

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قمنا بدراسة استطلاعية حول وقوع الحمى الرثوية الحادة لدى الأطفال بين سن الخامسة والرابعة عشر في دولة الكويت على مدار خمس سنوات (١٩٨٤ - ١٩٨٨م). كان متوسط الوقوع السنوي خلال مدة الدراسة ٢٩ / ١٠٠٠٠٠٠ طفل. وجدنا انخفاضًا في معدل الوقوع من ٣٧ / ١٠٠٠٠٠٠ في سنة ١٩٨٤ إلى ٢٥ / ١٠٠٠٠٠٠ في سنة ١٩٨٨م. مثلت الحالات المعاودة للحمى الرثوية الحادة لدى الأطفال نسبة ٢٧٪ في سنة ١٩٨٥م، علمًا بأن هذه النسبة انخفضت إلى ١١٪ في سنة ١٩٨٨م.

The incidence of acute rheumatic fever in children aged 5–14 years in Kuwait was studied prospectively over a period of five years (1984 through 1988). The mean annual incidence in the study period was 2.9/100,000 children. There was a decline in the incidence from 3.7/100,000 in 1984 to 2.5/100,000 in 1988. Twenty-seven percent of children with acute rheumatic fever presented as recurrences in 1985; this also declined to 11% in 1988.

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) remain to be major causes of death and disability in the Arab countries [1–11]. A program for prevention and control of ARF and RHD based on epidemiological surveys of the various aspects of the hemolytic streptococcal problem in the community should be considered. Data on the incidence of ARF in the Arab World are sparse [8,11]. The main purpose of this five-year prospective study was to estimate and monitor the annual incidence of ARF in Kuwait.

Patients and Methods

Kuwait is a small Arab subtropical country, located between latitudes 28° 45– and 30° 05– North of the Equator [12].

For the prevention of ARF, a National Committee was established. The committee included two cardiologists, an epidemiologist, two leaders from the primary health care service and chairmen of the pediatric departments of the five regional hospitals in Kuwait serving the whole population. The committee declared ARF as a registrable disease. Physicians in the primary health care centers were instructed to refer any child with a possible diagnosis of ARF to the pediatric department of the regional hospital where the diagnosis was verified.

Throat cultures and the antistreptolysin O (ASO) titers were performed as previously described [13]. An ASO titer of 333 or higher was considered to be elevated [13].

Once the diagnosis of ARF was confirmed and the child was ready for discharge from the hospital, the child and his family were instructed to start continuous secondary prophylaxis with monthly intramuscular Benzathin Penicillin G. The dose was 1.2 million units for children aged six-years or older and 600,000 units for children younger than six-years. Each child was provided with a special "rheumatic fever prophylaxis booklet". Injections were given in the primary health care center where the nurse in charge confirmed the date and signed the booklet. The booklet contained enough space for five years after which when completed was stored in the child's file and a new

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booklet provided. Social workers associated with primary health care clinics proved to be helpful in the success of the program. Patients were seen in the hospital clinic at least once every 3–6 months. During each visit, a detailed history was recorded with special attention to recurrence of symptoms and compliance with prophylaxis. Children who escaped carditis in the initial attack were given prophylaxis for five years; whereas children who had carditis and/or chorea in the initial attack were advised to continue with prophylaxis until the age of 25 years or longer if possible [2,10].

Diagnostic Criteria

A diagnosis of ARF was made according to the Revised Jones Criteria [14]. Diagnosis of arthritis and carditis were made as previously described [1,2]. Children with confirmed diagnosis of ARF were entered in the ARF registry of the committee.

Results

The 1985 census showed a general population of 1,697,301 of whom 382,885 (23%) were children between the ages of 5–14 years. Of these children 199,133 were Kuwaiti and 183,752 were non-Kuwaiti Arabs. Over the period of five years (1984 through 1988), 557 cases of ARF were diagnosed; 291 (52%) were boys and 266 (48%) were girls. All patients were hospitalized. Table 1 shows the annual incidence of ARF over the period of study. Table 2 shows the number of children who presented with the initial attacks and those who presented as recurrences. Table 3 compares the incidence of ARF with various countries.

Discussion

Kuwait is in a very unique situation of a "developing" country which, through the discovery of oil, had suddenly become rich; however, the problems of the developing countries including ARF and RHD are still prevalent. Data from our study show that the mean annual incidence of ARF in Kuwait over a period of five years is 2.9/100,000 children aged 5–14 years (Table 1). The incidence is unacceptably high especially when compared with those from the developed countries (Table 3). However, our data also show a declining incidence of ARF from 3.7/100,000 in 1984 to 2.5/100,000 children in 1988. The declining incidence over a period of five years is probably too short a time span for any reliable explanations or conclusions to be made. However, the association of the

TABLE 1. *The annual and mean annual incidence of ARF in Kuwait 1984–1988.*

	Kuwaiti		Non-Kuwaiti		Total	
Year	No.*	Incidence**	No.*	Incidence**	No.*	Incidence**
1984	57	29	86	47	143	37
1985	36	18	82	45	118	31
1986	37	19	65	35	102	27
1987	38	19	62	34	100	26
1988	23	12	71	39	94	25
Total	191	19***	366	40***	557	29***

* No of cases.
** Annual incidence/100,000 children (5–14 years).
*** Mean annual incidence (over 5 years).

TABLE 2. *ARF* in Kuwait in 1984–1988: initial attacks and recurrences.*

	Initial Attack		Recurrence		Total	
Year	No.	(%)	No.	(%)	No.	(%)
1984	114	(80%)	29	(20%)	143	(100%)
1985	86	(73%)	32	(27%)	118	(100%)
1986	79	(77%)	23	(23%)	102	(100%)
1987	82	(82%)	18	(18%)	100	(100%)
1988	84	(89%)	10	(11%)	94	(100%)
Subtotal	445	(80%)	112	(20%)	557	(100%)

* ARF = acute rheumatic fever.

TABLE 3. *Comparison of the incidence of ARF* in different countries.*

Country (reference)	Year of study	Age groups (years)	Incidence per 100,000 population
Kuwait (present study)	1984–1988	5–14	29
Saudi Arabia (8)	1980–1984	5–14	22
Sweden (15)	1971–1980	0–15	0.2
U.S.A. (16)	1960–1964	5–19	24
U.S.A. (17)	1977–1981	5–17	0.6
Iran (18)	1975	All ages	59–100
Czechoslovakia (18)	1972	1–15	8.5

* ARF = acute rheumatic fever.

declining incidence and increased improvement in the socioeconomic status and availability of better health care facilities recently achieved in Kuwait cannot be ignored. Better housing with a decrease in crowding was best achieved among Kuwaiti families. This has been reflected by the findings that the incidence was lower in Kuwaiti children than in non-Kuwaiti children and that the decline was more rapid and obvious in Kuwaiti children (Table 1). Two previous studies from Kuwait noted the virtual absence of ARF in wealthy residential areas and that a higher incidence of ARF in the other residential areas in Kuwait was found to be closely related to the socioeconomic status and the number of people per room [19,20]. Furthermore, a recent study from Saudi Arabia showed that the prevalence of RHD was higher in rural than urban areas in the country (4.4/100,000 versus 2.2/100,000) which has been ascribed to "the urban population in Saudi Arabia enjoying a higher standard of living and more social security than those living in rural areas; there is also easier access to medical care" [7]. The study also showed that the prevalence of RHD in schoolchildren was 0.5/100,000 in children from the high socioeconomic level versus 5.8/100,000 in children from the low socioeconomic level [7]. However, it should be stressed that overcrowding and poor socioeconomic status are not the only factors related to the incidence and epidemiology of ARF. Other known factors related to the host, the etiologic agent, and the use of antibiotics also influence the incidence of ARF [18]. Other unknown factors may also play a role [21].

The decline in the incidence of ARF in Europe and the USA over the last 50 years has been dramatic. In the Western European countries, the decline became more pronounced after the second world war, falling to an annual incidence of 1.2/100,000 in Denmark by 1962 and 0.2/1,000,000 in Sweden by 1986 [15]. However, ARF remained a significant problem in the USA during this period with an annual incidence of 2.6/100,000 children in Baltimore, Maryland, USA by 1964 [16]. Acceleration of the decline in the USA began in the late 1960s and by 1980, an annual incidence of 0.5/100,000 children was recorded in Baltimore, Maryland, USA [17]. However, in the recent outbreaks of ARF in the USA during the mid 1980s, the patients, primarily children, were surprisingly from the middle and upper socioeconomic classes [21]. This clearly illustrates that improvement of the socioeconomic status alone cannot totally explain the decline and return of ARF in the USA. Analysis of the factors possibly responsible for this phenomenon remain beyond the scope of this report [21,22].

The finding that 27% of our patients presented as recurrences in 1985 versus 11% in 1988 reflects the success of the program of secondary prevention in the country. The program was based on long-term continuous antibiotic secondary prophylaxis.

Acknowledgment

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COMPLIANCE IN SAUDI EPILEPTIC PATIENTS: DETERMINANTS OF COMPLIANCE IN SAUDI EPILEPTIC PATIENTS

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أجريت دراسة مدتها عام واحد (من يوليو ١٩٩٠م إلى يونيو ١٩٩١م) على مئة وأربعة أشخاص سعوديين يعانون من الصرع (تتراوح أعمارهم بين ١٥ و٤٥ عامًا) لتقييم مدى مواظبتهم على تناول العقاقير المضادة للصرع والعوامل المؤثرة على ذلك. كان ثلث المرضى (٨, ٣٠٪) غير مواظبين. طبقت معادلة تراجع على البيانات التي تم جمعها. كان تدني مستوى التعليم والتأثير السيء للمرض على المرضى من أهم عوامل قلة المواضبة. أما السن والجنس والحالة الشخصية وتاريخ الأسرة ومدة النوبة ونوعها فلم يكن لها دور مهم في المواظبة على العقاقير المضادة للصرع.

A one year prospective study was conducted (July 1990 to June 1991) on 104 Saudi epileptic patients (aged 15 to 45 years) to assess the degree of anti-epileptic drug (AED) compliance and factors that influence their compliance. One-third of the patients (30.8%) were non-compliant (NC). A logistic regression equation compared the data indicated. A low level of education and adverse effect of the disease on patients were the most important significant factors for poor compliance. Age, sex, marital status, family history, duration and type of seizure were not found to have a significant role in the patients' compliance to AED.

Patients who fail to comply with their medication are a source of constant confusion and frustration to doctors, but rarely has the problem of noncompliance (NC) been dealt with in any great detail. Antiepileptic drugs (AED) have a major role in the control of epileptic seizures. However, failure to take medication in the prescribed standard fashion may result in the loss of the treatment's efficacy. This may in turn lead to the administration of additional drugs and involvement of unnecessary diagnostic procedures or hospitalization to the patient. Non-compliant patients are a major source of financial concern in terms of time, money and resources which may adversely affect the relationship between both patient and doctor. Appropriate diagnostic or therapeutic plans are not possible without consideration of such factors including patients' attitude, family and living circumstances, past and predictable future behavior. When these factors are not integrated into the decision making process, it is unlikely that management plans based only on technical considerations will be effective [1]. Although these problems have been recognized for centuries, only recently has it become an issue of great importance as reported by Griffith in 1990 [2]. This has been a problem identified by managers, planners and doctors, but it is surprising to note how few studies have been reported on this topic. The major intent of our study was to try and discover the extent of NC by epileptic patients and factors influencing this attitude.

Patients and Methods

This study was carried out on 104 epileptic Saudi patients without obvious mental or psychological disorders attending the epilepsy clinic which was established in 1984 at King Khalid University Hospital (KKUH). These patients represent various socioeconomic classes in Saudi Arabia. They are seen every 2–3 months regularly by an experienced neurologist. The patients may see a primary care physician should the need arise between follow-up visits. Free health services as

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well as medications are provided to patients [3]. From the beginning of the study until its conclusion, none of the 104 patients seen were lost to follow-up. The prospective study was carried out between July 1990 and July 1991 to assess the sex, age, level of education, type of seizure, family history, degree of control, in addition to the AED level, side effects of prescribed drugs, effect of epilepsy on the patients' social life such as early school drop out rate and unemployment. For the purpose of this study, compliance has been defined as the extent to which the patients' behavior in terms of medications coincide with the clinical prescription as noted by Eaton in 1981 [4]. With regard to the level of education, patients who had less than four years of formal education were considered as having low education while those who had four to nine years of formal education were considered to be moderately educated, and those with more than nine years of formal education were considered to be highly educated.

Patients were asked to bring the medication containers during every follow-up to the clinic where the quantity of drugs remaining were counted. Those patients who missed a total of three days' doses/month were considered to be non-compliant. This was devised specifically for the present study. On follow-up the blood level for each patient was checked for AED. Any patient who failed to show up for an appointment as scheduled was contacted by phone. In addition, patients were interviewed and assessed about their compliance and the reasons for NC. The main objective of the study was not discussed with any patient. The data obtained was computed and analyzed using SPSS PC software. The logistic regression model was used to describe the relationship between the outcome of the dichotomous variable–(compliance and non-compliance) and another set of independent variables called covariables.

Results

Table 1 shows the sociodemographic characteristics of these patients by compliance. Thirty-two (30.8%) patients were NC. The best level of compliance was found among those aged 25–35 years. It was determined that the level of education played a significant role in compliance. In those who were highly educated, (84.4%) were compliant while a lower level of education correlated with NC. The sex of the patient did not have any differential effect on compliance. We found married patients were less compliant than the non-married, but not at a statistically significant value. Table 2 shows various disease aspects and its management by compliance. Those patients who had a family history of epilepsy were more compliant than those without. Patients suffering from complex partial epilepsy for more than ten years' duration which was not controlled well and which had adversely affected the patients' academic performance due to frequent seizures showed the worst compliance. Those patients in need of more than one medication to control their seizures were found to be more compliant. Medications used in this study included phenobarbitone, phenytoin, carbamazepine and sodium valproate. The drug level in the patients were within the therapeutic range or below and no patient became intoxicated. Table 3 demonstrates the co-efficient and odds ratio from stepwise logistic regression of significant variables. The most contributory factor of compliance was education. As the level of education increased from illiterate (low) to secondary and university (high), compliance increased by more than double (odds ratio = 2.364). Those patients whose academic performance was not adversely affected by their disease were found to be more compliant (odds ratio = 1.665).

TABLE 1. *Relation of sociodemographic characteristics to compliance (N = 104).*

Characteristics	N	Compliant (%) 72	Non-compliant (%) 32
Age:			
<25	53	36 (67.9)	17 (32.1)
25–35	33	25 (75.8)	8 (24.2)
>35	18	11 (61.1)	7 (38.9)
Sex:			
Male	64	43 (67.2)	21 (32.8)
Female	40	29 (72.5)	11 (27.5)
Education:			
Low	18	9 (50.0)	9 (50.0)
Moderate	54	36 (66.7)	18 (33.3)
High	32	27 (84.4)	5 (15.6)
Marital Status:			
Single	52	37 (71.2)	15 (28.8)
Married	52	35 (67.3)	17 (32.7)

Table 4 shows the reasons for NC obtained by patients that were interviewed. The major reasons for NC were the disbelief in the value and need of adherence to the prescribed drug regimen. This is the patient's own decision which does not depend on the effect of medication or physician advice. The second major reason was forgetfulness.

Discussion

Anti-epileptic drugs have done a lot in controlling epilepsy during the past four decades. Each year huge sums of money and more time and effort have been expended on the study of the effects of drugs, yet little attention has been given to whether patients take the drugs as prescribed. Therefore, the present study is to make doctors and those involved in the health care of patients constantly aware of the possibility of non-compliance in an attempt at minimizing this condition.

We have shown that the majority of the patients complied with the prescribed AED. Many of the patients were highly motivated and appreciated that the consequences would have a serious impact on their well-being if they became non-compliant. With the recent improvement in the socioeconomic status and community health care services in Saudi Arabia, it is expected that there will be better utilization of the health facilities among the population [5]. Previous researchers discovered that neurological problems were previously seen by local healers [6,7]. But recently, belief in local healers is waning and most of the patients now seek the help of orthodox-trained practitioners [8]. Only those with a low level of education or whether the disease adversely affected the patient's academic performance were found to be associated with NC. It is hoped that better education may help patients become more receptive to health care education efforts. This in turn may lead to better compliance. At the moment, health care education is gaining wide acceptance as it is one of the most important elements of primary health care services in Saudi Arabia [9]. Other sociodemographic data such as age, sex, and marital status did not affect compliance. In addition, the use of medication as prescribed was not affected by the presence of family history of the disease, duration of disease, type of

TABLE 2. *Relationship of disease aspects to compliance: (N = 104).*

Disease	N	Compliant (%)	Non-compliant (%)
Family History:			
Present	11	9 (81.8)	2 (18.2)
Absent	93	63 (67.7)	30 (32.3)
Duration:			
<5	43	28 (65.1)	15 (34.9)
5–10	40	30 (75.0)	10 (25.0)
>10	21	14 (66.7)	7 (33.3)
Type:			
Complex partial	37	26 (70.3)	11 (29.7)
Primary generalized	61	41 (67.2)	20 (32.8)
Unclassified	6	5 (83.3)	1 (16.7)
Control:			
Yes	58	54 (93.1)	4 (6.9)
No	46	18 (39.1)	28 (60.9)
No. of Medications			
One	83	56 (67.5)	27 (32.5)
Two	21	16 (76.2)	5 (23.8)
Effect on life:			
Yes	20	10 (50.0)	10 (50.0)
No	84	62 (73.8)	22 (26.2)

TABLE 3. *Coefficient and odds ratio from stepwise logistic regression of significant variables. (Dependent variable = compliance status coded as 1 for compliance and 0 for non-compliance).*

Significant variable	Coefficient	Odds ratio	Level of significance
Constant	−0.462		
Education			
Moderate	0.056	0.9458	0.06
Low	0.860	2.364	
Adverse effect on life	0.503	1.655	0.07

P = level for removal and entrance of variables = 0.15, 0.10.

TABLE 4. *Reasons patients gave for non-compliance (N = 32).*

Reasons	Number of patient (%)
Never told to continue	1 (3.1)
Side effect	2 (6.3)
Ran out of supply	2 (6.3)
Forgot to take it	10 (31.2)
No need	17 (53.1)

epilepsy, level of control or the therapeutic regimen used.

It is worth noting that our patients continue to take their medication regularly, but were reluctant to do so when they were seizure-free and hence self discontinuation of AED was attempted by the patients. Doctors have provided evidence proving that poor compliance regarding treatment may reflect inadequate patient education [10,11]. It is suggested that continuous use of drugs should be encouraged at the time when the first prescription is provided and continuously reinforced on subsequent follow-up. Counselling patients and helping them become partners in their own health care may help them in making healthy choices when complying with medication prescribed to them. A part of the physician's role in patient health care education and counselling is to try to explain to patients that AED may control seizures, but may not cure them completely. Failure to comply with a prescribed regimen may lead to the return of seizures in dangerous circumstances such as during driving or operating machines. In addition, patients and family members should be educated about what to do during a seizure. In addition to monitoring blood levels, "pill counting" by a doctor on follow-up can be used as an adjuctive method of monitoring the degree of compliance. Other causes of NC include the side effects of prescribed drugs and exhaustion of the supply of tablets. These problems were seen in four patients only.

Acknowledgment

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EXPERIENCE WITH DUCTOGRAPHY (CONTRAST MAMMOGRAPHY) AT THE KING KHALID UNIVERSITY HOSPITAL, RIYADH, SAUDI ARABIA

Omolara M. Roberts, FRCR; Tajuddin Malabarey, FRCR

جرى تصوير القنوات الثدية (تصوير الثدي بالصبغة الظليلة)، باستخدام وسط ظليل ذواب في الماء، لدى ست وعشرين امرأة راجعن المستشفى بين شهري أغسطس ١٩٨٩م وسبتمبر ١٩٩١م بسبب نجيج الحلمة (افراز مرضي). تراوحت الأعمار بين ٢٩ و٧٥ وكان متوسط العمر ٤١,٧ سنة، وبحقن القنوات على الجانبين لدى مريضتين كان مجموع صور الأقنية الشدية ثماني وعشرين. كان الفحص بسيطاً تحملته المريضات بصورة حسنة، وأظهر الأسباب المستبطنة لإفرازات الحلمة بوضوح. كانت هناك خمس حالات ورم حليمي، وحالة ورم دموي واحدة، وحالة سرطانة داخل القنوات، وإحدى عشرة حالة توسع القنوات، وست حالات من المرض الكيسي الليفي وكانت النتائج في أربع حالات طبيعية. اتضح من هذه الدراسة أن تصوير القنوات الثدية مفيد في تقييم حالات نجيج الحلمة قبل الجراحة.

Twenty-six female patients who presented with nipple discharge between August 1989 and September 1991 underwent mammary ductography (contrast mammography) using water soluble contrast media. The ages ranged from 29 to 75 with a mean of 41.7 years. Two patients had bilateral duct injections giving a total of 28 ductograms. The examination was simple and well tolerated by patients. The underlying causes of nipple discharge were clearly demonstrated. There were five cases of papilloma, one hematoma, one intraduct carcinoma, 11 duct ectasia, six fibrocystic disease of which four were normal. Ductography was found to be useful in the preoperative evaluation of patients with nipple discharge.

Spontaneous nipple discharge from a non-lactating breast is abnormal and needs further investigation to determine the underlying cause. Hughes et al [1] report an incidence of 6.4% of the patients referred to the breast clinic in Cardiff, Wales while Threatt [2] found an incidence of up to 10% in a review of a documented series. However, according to Leis et al [3,4], spontaneous nipple discharge is the second most common reason for breast surgery in the United States, comprising 7.4% of all breast operations.

Ductography has been shown in the literature to be the investigative procedure of choice for preoperative evaluation of the patient with nipple discharge [1,5–8]. It has been found to be reliable in identifying the cause of nipple discharge and localizing it for accurate surgical excision. To our knowledge, there are no published studies on this topic in the Kingdom of Saudi Arabia. This paper reports our experience in ductography at the King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia.

Material and Methods

A total of 26 patients who presented to King Khalid University Hospital with spontaneous, non-lactational nipple discharge, irrespective of color, from a single orifice of either one or both breasts, forms the basis of this study. The ages of the patients and types of discharge are noted.

Baseline mammograms were obtained in the craniocaudal and medio-lateral views. Nipple discharge must be present at the time of ductography for the appropriate duct to be identified. The affected nipple and surrounding breast was sterilized and the duct containing discharge was isolated by applying gentle pressure around the nipple. Cook's sialography catheter was filled with low concentration water soluble contrast

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medium, 60% sodium iothalmate, and (Conray 280) taking care to expel all air bubbles. Injection continued until the patient was able to feel pressure or fullness but no pain. The injection should be terminated if there is any pain, as this indicates extravasation of contrast medium. About 0.5–2.5 ml was usually sufficient for adequate visualization of the duct system depending on the underlying pathology. The needle was strapped around the nipple and postcontrast mammograms obtained in the craniocaudal and mediolateral views with limited compression. The films were viewed immediately and additional views with repeat injections obtained, when necessary. Surgical and pathological correlation was determined for all patients with intraluminal lesions.

Results

The age distribution of the patients investigated was 29 to 75 years with a mean of 41.7 years. The majority (80.7%) of the patients were within the 30–49 age group.

Significant plain film findings were present in three patients; the patient with carcinoma who presented with nipple discharge only, and two others who presented with masses and nipple discharge (Figure 1).

Duct ectasia was the most common finding. This was present in 11 ductograms. Five of these patients presented with greenish or brownish color discharge, three with bloody and three with serous discharge. The central ducts were involved in most of the ductograms. There was involvement of the peripheral ducts as well on two ductograms (Figure 2). Only one patient presented with a palpable mass on clinical examination as well as on the mammogram.

Six ductograms demonstrated intraluminal lesions. Only one of these patients presented with a palpable mass which was also seen on the plain mammograms (Figures 1A and 1B). At histology, five were confirmed to be papillomas and one was due to a hematoma. All the lesions were located in the subareolar regions, usually in dilated ducts (Figure 3). All the patients presented with serous or bloody nipple discharge.

Fibrocystic disease was present in six ductograms. These were shown as either small cystic dilatations of the terminal duct lobular units (Figure 4) or irregular strictures and dilatation of the duct system. Three out of the six patients presented with serous or bloody discharge.

The only duct carcinoma in the series presented with bloody nipple discharge. Plain films showed evidence of carcinoma and there was ductal encasement and narrowing at ductography.

Four ductograms were normal and all presented with greenish or brownish color nipple discharge (Table 1).

Discussion

Benign breast lesions are the most common cause of nipple discharge in our series as has been previously reported in other series [2–7]. Although all types of nipple discharges are abnormal, the serous and bloody types are regarded as

TABLE 1. *Ductographic findings in relation to color of nipple discharge.*

	Ductographic findings		Color of nipple discharge			
	Number	(%)	Serous	Bloody	Others G or B	Pathological diagnosis
Carcinoma	1	3.6	–	1	–	1 Carcinoma
Intraluminal	–	–	–	–	–	–
Lesions	6	21.4	3	3	–	5 Papilloma
Diagnosed as:	–	–	–	–	–	1 Hematoma
Papillomas	–	–	–	–	–	–
Duct ectasia	11	39.3	3	3	5	–
Fibrocystic disease	6	21.4	1	2	3	–
Normal	4	14.3	–	–	4	–
Total	28	100	7	9	12	–

G = green; B = brown.

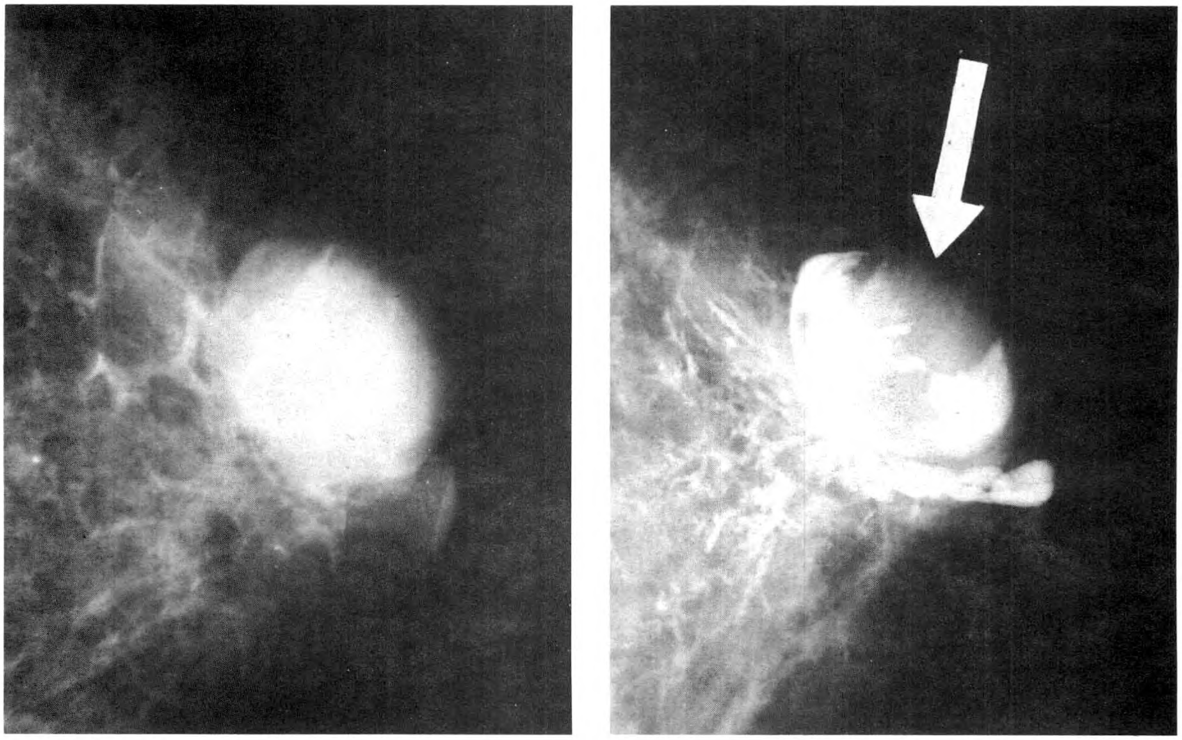

FIGURE 1. Papilloma. (A) Mammogram shows large round well defined mass adjacent to the nipple. (B) Ductogram—a dilated duct communicates with a cystic mass which contains a large filling defect. Histological diagnosis was papilloma.

being more significant as they are more often associated with hyperplastic duct lesions, like papillomas, papillomatosis, and carcinoma [1,3,4,7]. All papillomas and single carcinoma in the series presented with serous or bloody nipple discharge and none would have been overlooked had ductography been restricted to only these types of discharges. Five out of 28 (17.4%) of the ductograms were due to papilloma and one (3.6%) was due to carcinoma. The review of Tabar et al [7] of published ductographic series, reported an incidence range of 11–53% for papilloma and 4-20% for carcinoma. Our findings were at the lower end of this range. This was attributed to the fact that all types of nipple discharges were investigated in our series. In the case of the patient with carcinoma, ductography did not add to mammographic findings.

In 1930, Reis [9] was the first person to perform contrast mammography (ductography) and reported a breast abscess following injection of lipiodol into the mammary ducts. In 1938, Hicken et al [10] reported three cases of breast abscesses and two involving non-suppurating mastitis following the injection of thorotrast into the mammary ducts.

These complications as well as potential carcinogenic effects of retained thorotrast in the tissues led to the rejection of ductography as a diagnostic procedure. With the availability of water soluble contrast media, Funderbunk et al confirmed the safety of the procedure when he reported no complications in a total of 34 patients examined [11]. Clinical follow-up of the patients as well as pathological examination of excised specimens showed no evidence of chemical mastitis. This is because water soluble contrast agents which are quickly absorbed are not retained long enough to cause adverse chemical irritations such as lipiodol or radioactivity as thorotrast.

Some surgeons consider ductography to be time-consuming and of limited value in the investigation of nipple discharge [1,4,13] and proceed to operate after cytology. Evidence has shown that cytology is of limited use in the diagnosis of nipple discharge due to cancer. A false negative rate of 17.8% has been reported by Leis [4], while only 11% of cancer cases in Tabar et al's [7] series were positive by cytology. On the other hand, several colleagues have shown that ductography remains to be the only preoperative means of

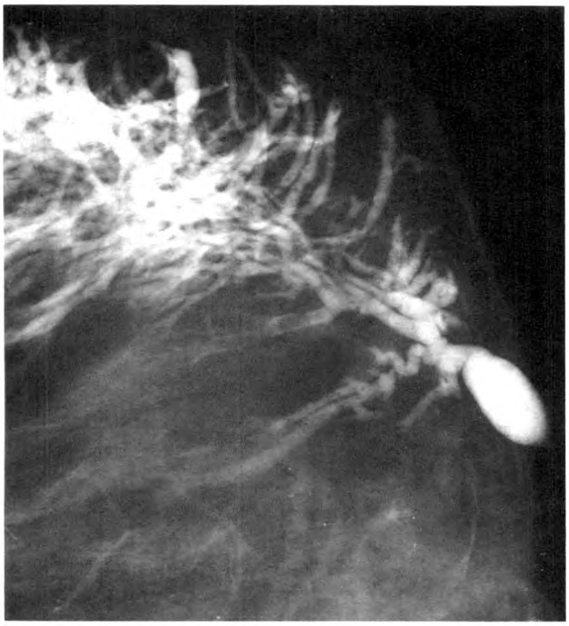

FIGURE 2. Duct ectasia involving the central and peripheral ducts. All outlined ducts are dilated.

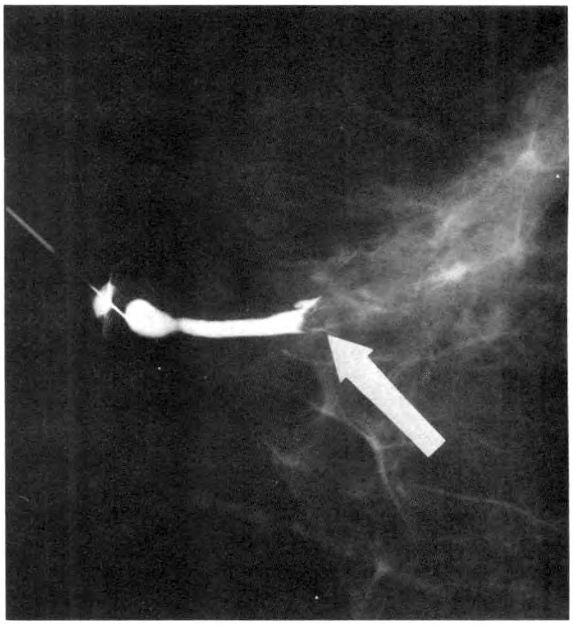

FIGURE 3. Dilated duct obstructed by an intraluminal lesion. Histological diagnosis was papilloma.

accurately identifying and localizing the cause of nipple discharge [5–7,11,12] since the majority of intraluminal lesions seen at ductography are neither clinically palpable nor seen on mammography because of their small size. The anatomical demonstration of the involved duct system permits the planning of appropriate surgical procedures such as central duct excision. The established management for nipple discharge is based on the assumption that the underlying pathologies are usually subareolar in position. However, duct ectasia, a common finding in nipple discharge, may extend peripherally in some patients (Figure 2).

However, in this case a different surgical approach may therefore be necessary. In addition, those with diffuse benign conditions such as fibrocystic disease or with normal findings at ductography are reassured and spared unnecessary surgery. Preoperative injection of methylene blue dye also makes identification of the pathological areas easy to visualize during surgery [7,13,14]. All intraductal lesions must be subjected to histological examination because of the inability of ductography to differentiate benign from malignant lesions.

Nipple discharge, especially serous or bloody types, is significant because of its association with breast cancer and pre-cancerous mastopathy. In the majority of cases, clinical examination and mammograms are negative. In these cases, ductography is indicated because of its ability to demonstrate the causative lesion, especially when intraductal.

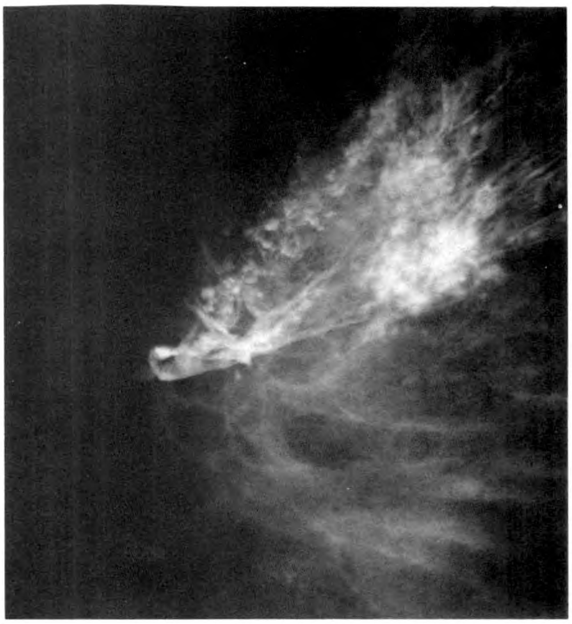

FIGURE 4. Fibrocystic disease – there are small cystic dilatations at the end of the terminal ducts.

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DETECTION OF HERPES SIMPLEX VIRUS DNA IN CEREBROSPINAL FLUID OF SAUDI PEDIATRIC PATIENTS WITH ENCEPHALITIS BY THE POLYMERASE CHAIN REACTION

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تبين باستخدام زراعة الخلايا وتهجين الحامض النووي بمسابير نوعية موسومة بالفوسفور المشع 32P لدراسة أثنتي عشرة عينة من السائل الشوكي لأطفال سعوديين أشتبه باصابتهم بالتهاب الدماغ أن النتائج كانت سلبية بالنسبة لحمة الحلأ البسيط. إلا أنه بعد تضخيم الدنا المستخلص من ١٠٠ ميكرولتر من كل عينة باستخدام مبدئات جينة البروتين السكري (د) لحمة الحلأ البسيط تبين أن سبع عينات كانت إيجابية لدنا حمة الحلأ البسيط. فيما بعد أكد التهجين باستخدام مسبار الدنا الموسوم إيجابية العينات السبع لحمة الحلأ البسيط، كما ظهرت إيجابية عينة أخرى، وبذلك أصبح إجمالي الحالات الإيجابية لدنا حمة الحلأ البسيط ثماني حالات. حسنت هذه الطريقة فرص اكتشاف حمة الحلأ البسيط في عينات السائل الشوكي، وقد تساعد في التشخيص المبكر لالتهاب الدماغ بحمة الحلأ البسيط.

Twelve samples of cerebrospinal fluid (CSF) from Saudi pediatric patients with suspected encephalitis were found negative for herpes simplex virus by cell culture and by nucleic acid hybridization using^{32}P-labeled specific probes. After amplification of DNA extracted from 100 μl of each sample using primers for the glycoprotein D gene of HSV, seven specimens were found positive for HSV DNA. Subsequent hybridization with the labeled DNA probe ensured the positivity of the seven samples and further detected one more positive sample, for a total of eight HSV DNA positive cases. This technique improved the detection of HSV in CSF samples and may assist in an early diagnosis for HSV encephalitis.

Herpes simplex virus (HSV) is one of the causative agents of viral encephalitis in children. Herpes simplex encephalitis (HSE) is usually diagnosed in cerebrospinal fluid (CSF) samples by virus culture and antigen detection [1,2], or by antibody level correlation with serum [3–7]. On many occasions, all these tests may be negative although clinical diagnosis may indicate HSV encephalitis [8]. This is probably due to latency of the virus, initiation of antiviral therapy or delayed reactions rather than an acute HSV infection.

Isolation of HSV or demonstration of HSV antigens in brain biopsies has been employed and is still felt by many to be the definitive diagnostic procedure [9,10]. However, this method is an invasive procedure with potential risks [11].

The advent of the polymerase chain reaction (PCR) by Saiki et al [12,13] has made it possible to amplify trace amounts of nucleic acids. The advantages and pitfalls of the PCR technology have been described in the literature [14,15]. For proper therapy to be quickly initiated [16], an improved and rapid laboratory diagnosis is necessary. Recent studies indicate that PCR technique followed by identification of the products by nucleic acid hybridization may offer a rapid method for the non-invasive detection of HSV encephalitis [17–21]. We employed this technology to demonstrate HSV DNA in CSF samples from Saudi pediatric patients.

Patients and Methods

Patients: Table 1 lists clinical diagnoses of our 12

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patients at the time CSF samples were sent for PCR procedure. Patient 3, who had thalassemia major, died of disseminated mucormycosis after acyclovir treatment for suspected HSE. All other 11 patients are alive although with varying degrees of neurologic handicaps, except for Patients 6 and 7 who are normal. CSF from Patient 10 was originally chosen as a control since he was a patient with a neurologic disease that was not thought to be encephalitis. CSF was clear in all specimens which were obtained from patients by lumbar puncture prior to treatment. All CSF specimens were found to be negative by cell culture method. CSF and sera were tested for the presence of anti-HSV antibodies using a Pharmacia-LKB ELISA kit (Uppsala, Sweden). Samples were assayed by dot blot hybridization and PCR without knowledge of the clinical details.

DNA Extraction: DNA was extracted as described by Aurelius et al [21] with minor modifications. Briefly, 100 μl of CSF was boiled for 15 min followed by the addition of 10 μl of 3 M sodium acetate, pH 5.2. The DNA was precipitated by the addition of 250 μl of 95% ethanol at -20°C for 1 h. The mixture was centrifuged at 14,000 rpm for 30 min at 4°C in an Eppendorf microcentrifuge. The pellet was washed once with 70% cold ethanol, vacuum dried and resuspended in 20 μl of sterile distilled water.

TABLE 1. *Working diagnosis, treatment, and outcome of 12 Saudi patients.*

Patient	Clinical diagnosis	Acyclovir treatment	Outcome
1	Gangliosidosis ? Encephalitis ?	No	Alive
2	HSE[a] (recurrent)	Yes	Alive
3	Disseminated mucormycosis HSE ?	Yes	Dead
4	HSE	Yes	?[a]
5	HSE	Yes	?[a]
6	Viral syndrome Encephalitis ?	No	Alive
7	Encephalitis ? Addison Disease	No	Alive
8	Rasmussen encephalitis	Yes	Alive (Focal status)
9	HSE	Yes	?[a]
10	Peliazaeus-Merzbacher Disease	No	Alive
11	HSE (recurrent)	Yes	Alive (chorea)
12	HSE (recurrent)	Yes	Alive

[a] Patient failed to show for follow-up.

Primers and Probes: Two sets of nested primers and an oligonucleotide probe were selected in the glycoprotein D gene as described previously [21]. The first round of PCR was carried out using the outer set of primers followed by a second round of amplification with the inner set. Sequences of primers and probe are listed in Table 2 and were custom-synthesized by Research Genetics Inc. (Huntsville, AL, USA).

Controls and Precautions: A positive control of purified HSV-1 virus particles and a negative control of PCR reaction mixture were included. Recommendations of Kwok and Higuchi [22] were strictly followed to avoid contamination. Only positive displacement pipettes were used. Preparation of DNA samples was performed in a separate room from that of PCR analysis.

PCR: The nested PCR technique was performed under standard conditions in 0.5 ml polypropylene tubes with a model 480, programmable DNA thermal cycler (Perkin Elmer-Cetus, Norwalk, CT, USA). The reaction mixture contained 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 1.5 mM MgCl$_2$, 0.01% gelatin, 0.2 mM of each of dNTP (dATP, dGTP, dCTP, and dTTP), 0.2 pmole of outer primers, 1.25 U of native *Taq* DNA polymerase, and 10 μl of CSF DNA extract in a final volume of 50 μl. The mixture was overlaid with 50 μl of light mineral oil to prevent evaporation. The first round of PCR amplification was performed for 20 cycles using the following cycling parameters. An initial denaturation step of 95°C for 10 min was followed by melting at 95°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 30 sec. The second round was carried out by adding 20 pmoles of inner primers and 1.25 U of native *Taq* DNA polymerase for 30 cycles. The same cycling conditions were used in round 2 except that the final extension step was increased to 5 min. One hundred picograms of purified HSV-1 (strain F) DNA was included as a positive

TABLE 2. *Sequence of synthesized oligonucleotide primers and probe used in the study.*

Primer and probe	Genomic location	Sequence (5′ – 3′)
Outer primers:		
HSVPR3	19–43	ATCACGGTAGCCCGGCCGTGTGACA
HSVPR4	218–239	CATACCGGAACGCACCACACAA
Inner primers:		
HSVPR5	51–71	CCATACCGACCACACCGACGA
HSVPR6	166–188	GGTAGTTGGTCGTTCGCGCTGAA
Probe:		
HSVPB2	96–125	TACGAGGAGGAGGGGTATAACAAAGTCTGT

control, as well as a reagent control with no template DNA. Amplified products (10 μl) were analyzed on 2% agarose gel electrophoresis in TBE buffer (90 mM Tris base, 90 mM boric acid, 2 mM EDTA, pH 8.3), stained with ethidium bromide (1 μg/ml), and photographed under UV light.

TABLE 3. *Outcome of various tests performed on CSF samples from pediatric patients with encephalopathy for the detection of HSV.*

		Tests performed on CSF			
Patient	Sex/Age	Culture	Antibody titer	DNA probe[a]	PCR
1	F/7 mo	–	–	–	–
2	M/10 mo	–	+	–	–
3	F/14 yr	–	+	–	+[b]
4	M/7 mo	–	–	–	+
5	M/6 mo	–	–	–	+
6	M/4 mo	–	–	–	+
7	M/3 yr	–	–	–	–
8	M/11 yr	–	–	–	–
9	F/11 mo	–	–	–	+
10	M/11 mo	ND[c]	ND	–	+
11	F/3 mo	ND	+	–	+
12	M/7 yr	–	+	–	+

[a] Dot blot hybridization was used before PCR amplification.

[b] PCR products seen only after hybridization with specific probes.

[c] Not done.

Dot and Southern blot analysis: For dot blot, 10 μl of each of CSF DNA extract before amplification and of the amplified products were denatured by boiling for 10 min, chilled on ice, and applied onto a zeta probe membrane using a manifold apparatus (Bio-Rad Laboratories, Richmond, CA, USA). For Southern blot, the amplified PCR products which were electrophoresed on agarose gels were transferred onto a zeta probe membrane (Bio-Rad Laboratories, Richmond, CA, USA). The membranes were air dried and baked under vacuum at 80°C for 2 h. Internal oligonucleotide probe (25 pmoles) was labeled at the 5' end with gamma-^{32}P [ATP] (30000 Ci/mmol, Amersham International, Buckinghamshire, England, UK) using polynucleotide kinase (BRL, Gaithersburgh, MD, USA) and purified on Sephadex G-50. Hybridization was carried out at 42°C for 16 h in 10 ml of 6X SSC (1X SSC is 0.15 M NaCl, 0.015 M sodium citrate), 5X Denhardt's solution (1X Denhardt's solution is 0.02% bovine serum albumin, 0.02% polyvinylpyrrolidone, 0.02% Ficoll 400), 0.5% SDS, 50% formamide, and 100 μg/ml heat denatured salmon sperm DNA. The membrane was then washed four times for 5 min each in 50 ml of 2X SSC containing 0.1% SDS at room temperature and twice for 15 min each in 2X SSC containing 0.1% SDS at 50°C. The membrane was air dried and exposed overnight to a Kodak x-ray film (XK-6) with intensifying screen at –70°C.

Results

Laboratory findings regarding the detection of HSV are summarized in Table 3. Ten CSF samples were tested for HSV growth in cell culture. No cytopathic effect was evident and no viral antigens were detected as assessed by fluorescein labeled anti-HSV monoclonal antibodies. Two CSF and their corresponding sera were positive for anti-HSV antibodies with relatively high titers.

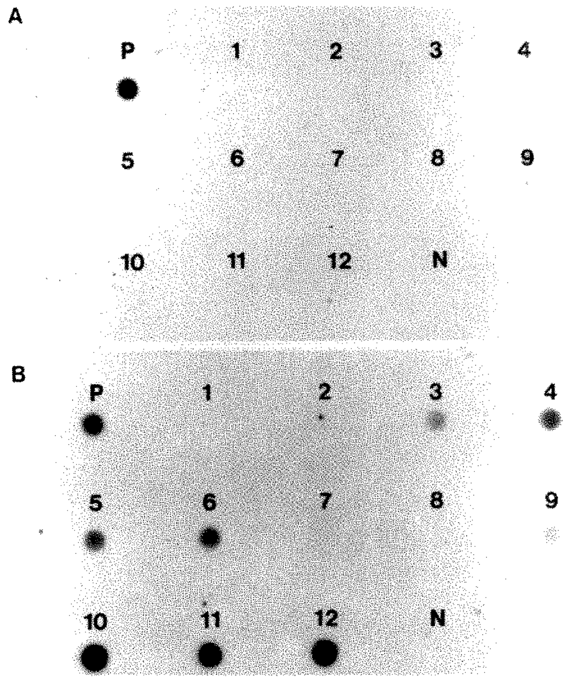

FIGURE 1. Dot blot hybridization on CSF samples (1-12) from pediatric patients suspected with encephalitis using HSV labeled oligonucleotide probe before (Panel A) and after (Panel B) PCR amplification. P and N represent positive and negative controls, respectively.

The remaining CSF samples were all negative for anti-HSV antibodies but their corresponding sera contained low titers. All samples were subjected to dot blot hybridization with^{32}P-labeled DNA probe specific for HSV before PCR amplification and were found negative for HSV DNA (Figure 1A). After DNA amplification, seven of the samples were positive for HSV DNA as shown by electrophoresis of the amplified products on 2% agarose gel stained with ethidium bromide without subsequent hybridization by either dot or Southern blot (Figure 2A). We performed hybridization technique for the amplified products in order to detect any positive signal for the other five samples and to assure the specificity of the obtained signals. Figure 1B shows dot blot and Figure 2B shows Southern blot hybridization results after amplification. This assured the specificity of the amplified product and increased the sensitivity of detection as sample 3 was shown to be positive for HSV DNA. Therefore, eight CSF samples from our 12 pediatric patients with encephalitis were found positive (66.7%), while the rest were negative.

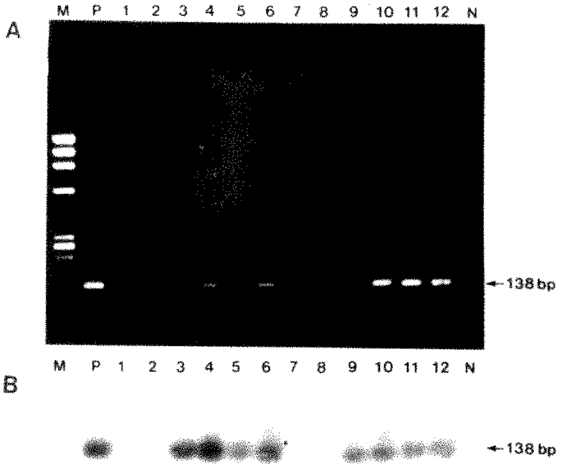
M P 1 2 3 4 5 6 7 8 9 10 11 12 N
A
←138bp
M P 1 2 3 4 5 6 7 8 9 10 11 12 N
B
←138bp

FIGURE 2. Agarose gel electrophoresis of PCR amplified products from CSF samples (1-12) from pediatric patients suspected with encephalitis stained with ethidium bromide (Panel A) and after Southern blotting (Panel B). M, P, and N represent φ X 174/HaeIII molecular weight markers, positive control, and negative control, respectively. The number on the right indicates the size of the PCR amplified product.

Discussion

In this study, we report the use of PCR for the detection of HSV in CSF from cases suspected with HSE. The specimens we have used were from patients with encephalopathy, but strongly suspected for HSE clinically, not from patients with diagnostically confirmed HSE. The cellular nature of the infection makes it extremely difficult to grow virus from CSF, but not from brain tissues. Therefore, brain biopsy is accepted as the definitive method for diagnosis of HSE [23], mainly by growing the virus in cell culture. The four PCR-negative samples (Patients 1,2,7, and 8) are all probably true negatives. Of the eight PCR-positive samples (Patients 3–6 and 9–12), one was not clinically suspected to have encephalitis (Patient 10). He was one of two siblings with a chronic, progressive dementing disease, with spastic paralysis after infantile-onset nystagmus, whose brain biopsy showed a spongiform leukoencephalopathy but was not investigated for HSV. However PCR technique showed positivity for HSV DNA in his CSF. It is interesting that the one patient who had brain biopsy (Patient 2), which was negative for HSV by EM and cell culture, was also negative by PCR, even though the patient's clinical history, neurologic examination, and CT and MRI scans strongly suggested the possibility of HSE. This patient did not improve neurologically after two courses with acyclovir.

Our results show that HSV DNA can be demonstrated in small CSF samples of patients with encephalopathy by PCR amplification and hybridzation of the products with specific probes. It appears that samples positive for HSV did not contain enough virus particles to support virus culture or antiviral antibody production. In addition, the extremely low copy number of HSV DNA in the samples did not enable the detection of the DNA by hybridization with the specific probe until after PCR amplification. The primers that we used were optimal for the detection of HSV-1, although slight cross reactivity with HSV-2 was reported [21]. Therefore, we assume that the viral DNA detected by PCR was that of HSV-1 and those that were negative could contain either HSV-2 or other viruses. Our findings are in agreement with previous reports [8,21,22,24] showing the efficacy of PCR methods in confirmation of possible involvement of HSV in such cases. Experiments to investigate the presence of nucleic acids of other neurotropic viruses are in progress.

Acknowledgment

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Case Reports

BRUCELLA PNEUMONIA: A CASE REPORT

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Brucellosis is a classical zoonosis caused by a gram-negative bacillus of the genus Brucella. It is endemic in Saudi Arabia [1], and considered to be a major health problem in this country [2,3]. Human brucellosis can either be acute or chronic, and presents with a variety of manifestations. The majority of patients present with pyrexia and musculoskeletal involvement [1–4]. This disease may also be complicated by the involvement of various systems in the body including cardiovascular, central nervous and genitourinary systems [5,6].

Pulmonary brucellosis, on the other hand, is a rare complication [5,7]. A number of cases were reported in 1983 in a study of a spectrum of pneumonia found in Riyadh [8] indicating no details on the clinical picture or response to therapy. Brucellar pulmonary involvement has been reported in Kuwait [7,9,10]. We report a case of brucellar pneumonia with positive sputum culture. To the best of our knowledge, this is the first case to be reported from the Middle East with positive sputum for brucellosis.

Case Report

A 75-year-old retired Saudi male was admitted with a two-week history of cough, productive of yellowish sputum and difficulty in breathing. The patient was known to have had chronic obstructive pulmonary disease (COPD) for ten years and hypertension of one year's duration. The patient has been a chronic smoker for more than 30 years. He used to go to the Outpatient Department (OPD) for follow-up for his chest problem. A few months prior to admission he experienced shortness of breath on exertion. This illness was preceded by rhinorrhea of one day's duration when he started to have fever, productive cough and shortness of breath at rest. The patient presented with no history of raw milk ingestion or contact with domestic animals. Examination revealed a patient in moderate respiratory distress but not cyanotic. His temperature was 37.5°C, pulse was 112/min and regular, respiratory rate was 40/min and his blood pressure was 140/90 Torr. The neck was supple with no cervical lymphadenopathy and no lymph node enlargement was noted. Respiratory system examination revealed a symmetrical movement of the chest with intercostal retractions and increased anteroposterior diameter; tactile vocal fremitus was increased in the right infra-axillary area; breath sounds were vesicular with scattered rhonchi and crepitations which were more prominent and coarser at the right base. Cardiovascular system examination was normal apart from tachycardia. Abdominal examination showed no organomegaly. Musculoskeletal system showed no peripheral or axial skeletal involvement.

Investigations revealed WBC – 9.6 × 10^9/L, Hb – 12.7 gm/dl, platelet – 443 × 10^9/L, Na+ – 120 mmol/L and K+ – 4.1 mmol/L. His chest radiograph revealed a peripheral infiltrate at the right lower zone with bilateral lung hyperinflation (Figure 1). The blood culture was sterile following seven days of incubation, while the sputum culture was initially reported to have gram-negative cocco bacilli suggestive of *Haemophilus influenzae* but later, the organism was identified as *Brucella species* because it was a gram-negative rod, nonmotile, carboxyphilic, catalase positive, oxidative positive and urease positive. This was further con-

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firmed by a full biochemical reaction [11]. Further differentiation could not be performed due to limited resources. The organism was found to be sensitive to tetracycline, cotrimoxazole, amoxicillin-clavulanate, chloramphenicol, ceftriaxone and rifampicin. Blood culture and serology for brucellosis were performed eight days following admission upon the confirmation of the sputum result. The blood culture was sterile following 50 days of incubation in Bactec NR 6A bottle (enriched soybean casein digest broth with CO_2), at 37μC, and read on Bactec NR 660 (Becton Dickenson). Subcultures were made on blood agar, chocolate agar and Macconkey agar, incubated aerobically with 7% CO_2. The brucella titer by latex agglutination (Crescent Diagnostic, Jeddah, Saudi Arabia), was 1/80 for *B. abortus* and 1/40 for *B. melitensis*. One month later, a repeat titer showed a decrease to 1/20 to *B. melitensis* and was negative for *B. abortus*.

Hospital Course

The patient was initially treated as a simple chest infection with exacerbation of his COPD. A third generation cephalosporin ceftizoxime 1gm q 12 hrs by IV route was started. The patient showed significant improvement and the sputum became whitish. He was discharged from the hospital after six days of treatment with ceftizoxime on amoxicillin-clavulanate (augmentin). When the results of the sputum were obtained, he was recalled for re-evaluation and modification of treatment. The patient had already improved symptomatically but his chest radiograph remained abnormal (Figure 2). He was then started on a course of sulfamethoxazole 800 mg and trimethoprim 160 mg twice a day for a total of six weeks. Thirty days following discharge, the patient improved markedly and the chest radiograph abnormality was clear (Figure 3).

Discussion

Pulmonary brucellosis is rarely reported even from the highly endemic areas [7,10,12]. This may be due to the fact that respiratory symptoms are mild and are overshadowed by other features of the disease or may even be misdiagnosed as flu [13]. Pulmonary brucellosis probably occurs through inhalation of the brucella organism, as inhalation is a known route of acquiring brucella infection [7,14]. Respiratory involvement of brucellosis presents with diverse manifestations, the most common of which may be dry or productive cough. Other manifestations include: bronchitis, bronchopneumonia, solitary or multiple lung nodules, lung abscess, soft miliary shadow-

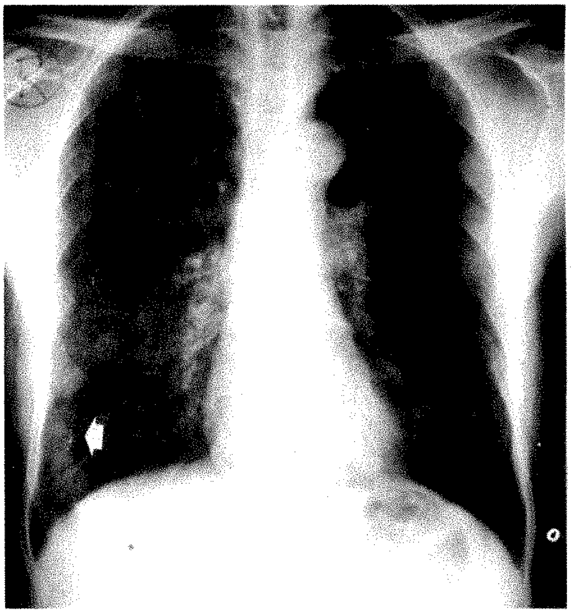

FIGURE 1. Postero-anterior chest radiograph on admission showing a peripheral infiltrate at the right lower zone (arrow).

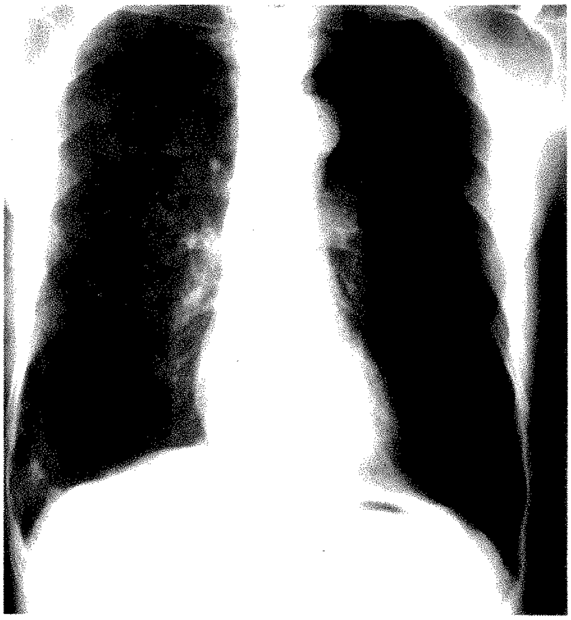

FIGURE 2. Postero-anterior chest radiograph six days after admission showing the same findings as in Figure 1.

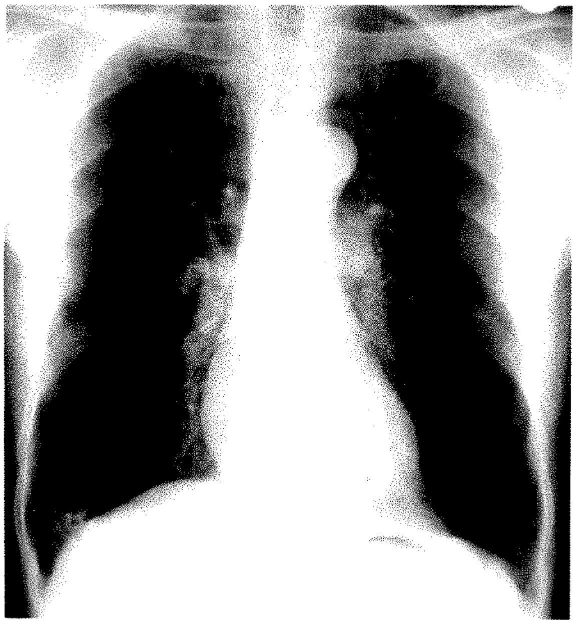

FIGURE 3. Postero-anterior chest radiograph 30 days after discharge with resolution of the pulmonary infiltrate at lower zone.

ing, hilar and paratracheal lymphadenopathy and pleural effusions [7,13]. Diagnosis of this complication depends primarily on serologic tests and titers of at least 1:320 have been detected in most cases of pulmonary brucellosis [7,10]. However, the relatively low titer detected in our patient may be explained in two ways: the elderly patient could be one of those who are "poor reactors" to antigenic stimuli, similar to those who respond poorly to vaccines, such as hepatitis B vaccine. Another explanation may be that the patient was treated very early, that no time was allowed for the antibody titers to rise markedly. Furthermore, serologic tests are the only indirect evidence of the infection. Isolation of the organism from blood and other body fluids remains the golden standard for diagnosis. However, blood cultures are known to be positive in about 50% of cases [2,7]. Brucella organisms have been isolated from pleural aspirate [10,12] and sputum [15]. In our case, the sputum was positive for *Brucella species* and the possibility of contamination in the laboratory was ruled out, as no brucella organisms were isolated around the same time from other samples. Chest radiograph findings are not specific and include soft miliary mottling, parenchymal nodules, consolidation, chronic diffuse changes, hilar and paratracheal lymphadenopathy and pneumothorax [16]. To our knowledge, no case of pulmonary brucellosis with positive sputum culture has been reported from Saudi Arabia. However, cough associated with acute brucellosis has been reported by other investigators [12,16], and two cases of pneumonia have been attributed to brucella infection [8].

Patients with COPD with acute exacerbations are usually presumed to have chest infection. In many instances, these infections are due to either *streptococcus pneumoniae, H. influenzae,* or *Branhamella catarrhalis* and treated as such. However, in this patient *Brucella species* was the sole organism isolated. Third generation cephalosporins have been used in the treatment of human brucellosis with variable success [17,18]. However, their role has yet to be determined. Our patient improved significantly following six days of treatment with ceftizoxime. This may indicate that shorter courses rather than the conventional 4–6 weeks of treatment with tetracycline, streptomycin, rifampicin or cotrimoxazole may be sufficient when using a third generation cephalosporin as a single agent. Another interesting point is the lack of history of exposure to brucella by an obvious means. This is not unusual as the history of raw milk ingestion or dealing with animals varied widely from 27% to 87.6% in different series [2,3,19].

In conclusion, pulmonary brucellosis should be considered in the differential diagnosis of any pulmonary involvement in a patient from an endemic area for brucellosis. The necessary investigations for brucellosis should be considered by both clinicians and microbiologists. Despite the fact that there is limited experience with the use of cephalosporins in the treatment of human brucellosis, the literature available reported the use of cephalexin and showed "a modest therapeutic effect" [20]. Nonetheless, the role of third generation cephalosporins in the treatment of human brucellosis should be explored further, taking into consideration the very good *in vitro* activity of these agents against brucella organisms [20].

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METHEMOGLOBINEMIA INDUCED BY TOPICAL HAIR OIL

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The use of scientifically unproven, traditional medications and "over-the-counter" medications is a universal problem which often results in serious health hazards and delays in seeking appropriate medical treatment. These "medications" are usually taken because of traditional cultural beliefs in their therapeutic efficacy or in desperation by patients with chronic, serious and incurable illnesses [1–11].

A case of methemoglobinemia resulting from the external use of "over-the-counter" hair oil is presented in this report to alert treating physicians to the dangers of traditional medications and cosmetic preparations.

Case Report

A two-month-old male presented with a four-day history of bluish discoloration of the face and lips. On physical examination, he was found to have chocolate-colored central cyanosis, but was otherwise a healthy-looking infant with no evidence of pulmonary, cardiac or central nervous system disease. A venous blood sample was chocolate colored and the color did not change on exposure to room air and shaking. A blood sample was sent to the laboratory and the methemoglobin level was 31.5%. On further discussion, the mother admitted that she had rubbed the infant with "Oleum Dulcis" which is a locally available hair oil which is imported from India and contains a strong almond odor (Figure 1). On chemical analysis the Oleum Dulcis was found to contain one percent nitrobenzene but no benzaldehyde, nitrite, cyanide or lead. Additional laboratory investigations included: pH 7.45, PaCO$_2$ 33 mm Hg, PaO$_2$ 78 mm Hg, total CO$_2$ 22.8 mmol/L, oxygen saturation 95.9%, and hemoglobin 110 g/L. Chest x-ray, serum electrolytes, BUN, creatinine, glucose, hemoglobin electrophoresis and G$_6$PD

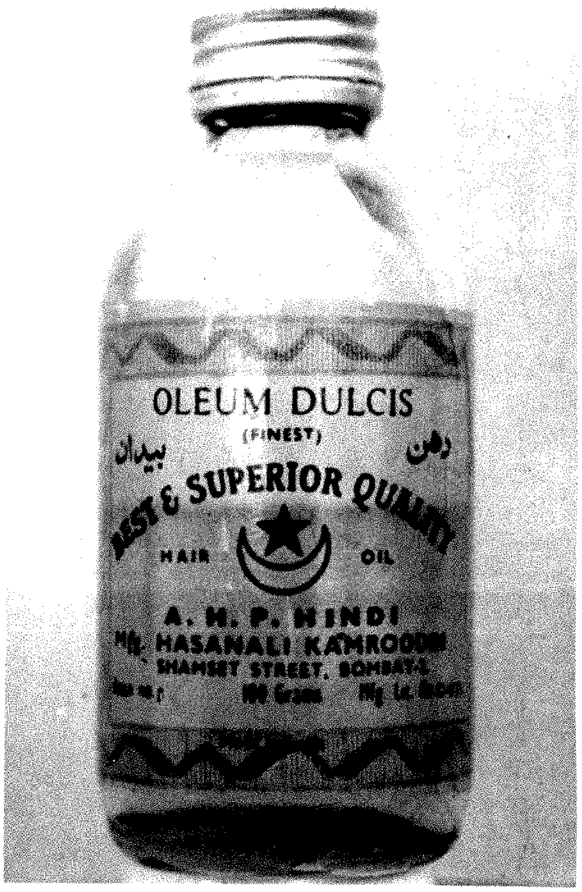

FIGURE 1. The container of Oleum Dulcis, a locally available hair oil with an almond-like smell and 1% nitrobenzene.

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were all normal. As the patient was asymptomatic apart from being cyanosed, he was observed without treatment. The methemoglobin level gradually dropped during the three day period. The patient was discharged in good condition and has had no problems on follow-up.

Discussion

Methemoglobin results when the ferrous iron of the heme is oxidized to the ferric form [12]. This hemoglobin is unable to bind with oxygen molecules. Normally, 1–2% of hemoglobin iron is present in the oxidized ferric form [12,13]. The balance between ferrous and ferric iron is mainly maintained by the enzymatic reduction of the oxidized ferric molecule by NADH-dependent methemoglobin reductase [12,13]. Hereditary methemoglobinemia results from a deficiency of NADH-dependent methemoglobin reductase or the presence of one of a group of unstable hemoglobins collectively called hemoglobin M [12].

Ingestion of [14,15], inhalation of [13], or contact with [16] certain oxidizing chemicals or drugs may lead to severe life-threatening methemoglobinemia in otherwise normal individuals. Although persons of any age [12,13] may be affected by methemoglobinemia, infants younger than five months of age are particularly susceptible because of their physiologically low level of NADH-dependent methemoglobin reductase [12,17–20]. In the United States, well water is probably the most important cause of acquired methemoglobinemia in formula-fed infants [18–20].

Methemoglobinemia should be suspected in any person with central cyanosis unresponsive to 100% oxygen therapy. A useful bedside diagnostic test of value while awaiting the definitive diagnosis is as follows: a drop of the patient's blood, which is usually chocolate brown in color, is placed on filter paper, exposed to room air and compared to blood from a control. Methemoglobin remains chocolate brown in color for a long time, even after exposure to higher oxygen concentrations.

PaO_2 is usually normal with a low level of "measured" oxygen saturation (the oxygen saturation value given by most blood gas analyses is calculated from the measured PaO_2 and does not represent the "true" oxygen saturation). Diagnosis of methemoglobinemia should be confirmed by checking the serum level of methemoglobin.

Our two-month-old patient was repeatedly rubbed with a locally available hair oil (Oleum Dulcis) which, on analysis, proved to contain nitrobenzene, which is rapidly absorbed from the gastrointestinal tract, skin or mucous membranes of the respiratory tract. The mean adult lethal dose has been estimated to be 1–5g. Symptoms of toxicity may be delayed between one and four hours. The clinical manifestations are mainly those of methemoglobinemia. Because nitrobenzene has an odor of bitter almonds, cyanide poisoning (which is common with exposure to bitter almonds) may be suspected and should be excluded.

Our case is an example of the serious health hazards which may result from the abuse of unsupervised preparations which are locally available. The need for public education cannot be over-emphasized.

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INFANTILE MALIGNANT OSTEOPETROSIS PRESENTING AS BILATERAL CHOANAL ATRESIA: REPORT OF TWO CASES

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Osteopetrosis is a rare disorder characterized by increased skeletal density and abnormalities of bone remodeling due to impaired lysosomal function of osteoclasts and their precursor cells, monocytes [1]. Two major forms of osteopetrosis, a benign autosomal dominant form, and a malignant autosomal recessive form, are recognized. The more common is the benign autosomal dominant form described by Albers-Schonberg in 1904 [2] which is compatible with a normal life span and is at times brought to the attention of physicians because of mild anemia, craniofacial disproportion or fractures. But in most instances, these cases are usually discovered accidentally on x-rays taken for unrelated problems. The less common autosomal recessive malignant form is characterized by severe clinical manifestations from early infancy and often progresses to an early death [3]. Clinical manifestations in such cases include bone marrow failure with anemia, bleeding diathesis, and susceptibility to infections. Two variants of autosomal recessive osteopetrosis have also been described: a mild form with various dysmorphic features described by Kahler et al [4], an osteopetrosis occurring in association with renal tubular acidosis described by Vainsel et al [5].

The rapidly progressive bone thickening associated with the malignant type of osteopetrosis often leads to encroachment of dense bone on the skull foramina and neural structures, resulting in proptosis, blindness, deafness, and other cranial nerve palsies [6]. Our search of the literature revealed only one previous instance of the occurrence of choanal atresia in association with osteopetrosis [7]. The present report describes the occurrence of congenital bilateral choanal atresia in two Saudi infants who had malignant infantile osteopetrosis. We believe that this association may be more common than previously recognized.

Case Reports

Patient 1

AA, a female neonate, was born to young Saudi first cousin parents in a peripheral hospital at 36 weeks' gestation. Her birth weight was 2.5 kg. Because of severe dyspnea and marked subcostal recession shortly after delivery, she was transfered to the Neonatal Intensive Care Unit (NICU) at King Khalid University Hospital (KKUH), Riyadh. Attempts at the NICU to introduce a nasal catheter through the nostrils were unsuccessful; a provisional diagnosis of bilateral choanal atresia was therefore made. Immediate management consisted of administration of oxygen through a headbox with an oropharyngeal airway in situ.

On examination, she looked pale and dysmorphic with a triangular face, depressed nasal bridge, and bilateral proptosis. The liver was enlarged to 4 cm and the spleen was 6 cm below the costal margins.

Laboratory investigations revealed a hemoglobin concentration of 6.9 gm/l, and white cell count (WBC) of 29.5 × 10^9/L with 23% neutrophils, 31% lymphocytes, 17% monocytes, 10% promyelocytes, 3% metamylocytes, 2% myelocytes, and 2% blast cells; the platelet count was 48 × 10^9/

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L. The liver function tests were normal and the serological screening tests for toxoplasmosis, rubella, cytomegalovirus, hepatitis and syphillis (TORCHS) infections were negative. Chest x-ray revealed normal lung fields, but the ribs and vertebrae were incidentally noted to be sclerotic. Subsequent skeletal survey revealed generalized increased bone density compatible with the diagnosis of osteopetrosis. Histopathology of the bone marrow biopsy which was performed later also supported the diagnosis of osteopetrosis. Diagnosis of bilateral complete choanal atresia of bony type was confirmed by a nasopharyngogram with contrast (Figure 1). Computed tomographic (CT) scan of the brain was normal, but both the visual evoked responses (VER) and auditory brainstem evoked responses (ABER) revealed significant impairment.

The bilateral choanal atresia was successfully treated surgically after correction of the baby's anemia. The respiratory difficulties abated, but the baby continued to require frequent blood transfusions and courses of antibiotics for the management of anemia and infections. She was considered for bone marrow transplantation, but died at home at the age of eight weeks before a suitable donor could be found.

Patient 2

BB, the first child of healthy Saudi first cousin parents was delivered normally at 38 weeks' gestation at KKUH following a pregnancy complicated by chickenpox during the second trimester. Ultrasound examination of the mother at 19 weeks' gestation was normal and serological screening tests for TORCHS were negative.

The baby required intermittent positive pressure ventilation from birth because of poor respiratory effort, bradycardia, and cyanosis. The birth weight, body length, and head circumference were all below the 10th centile for her gestational age. Striking craniofacial abnormalities noted at birth included prominence of the frontal and parietal skull bones which were separated by deep groves and widely separated cranial sutures. The anterior and posterior fontanelles were wide and measured 5 × 5 cm each. There was marked bilateral proptosis. The nose was small with a depressed septum, and the tiny nostrils were anteriorly directed (Figure 2). Attempts to pass nasal catheters through the nostrils revealed the presence of bilateral choanal atresia of bony type. There was marked narrowing of the thorax, while examination of the abdomen revealed enlarged liver and spleen that were palpable 4 and 3 cm below the right and left costal margins, respectively.

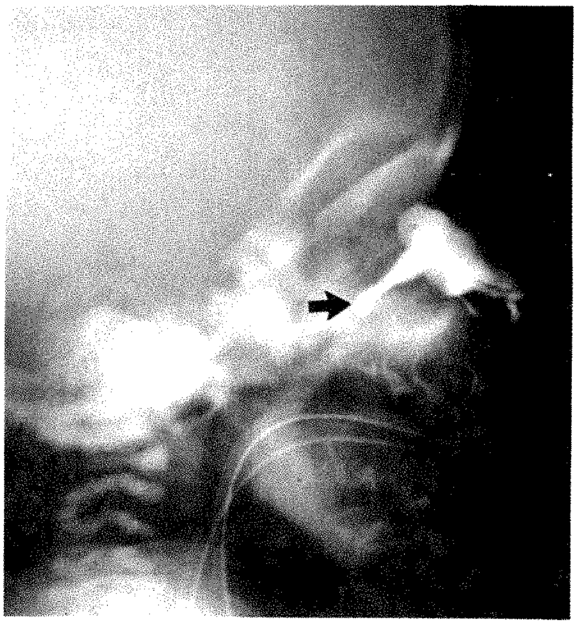

FIGURE 1. Lateral view of the nasopharyngogram showing choanal atresia (arrow).

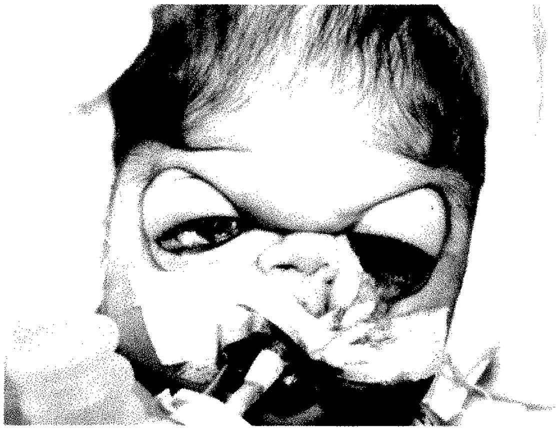

FIGURE 2. Facial features of patient 2 showing bilateral proptosis and depressed nasal septum.

A skeletal survey performed because of the severe dysmorphic features revealed features consistent with the diagnosis of osteopetrosis. Ultrasonography and computerized tomography of the brain also revealed extensive calcification involving the periventricular regions, thalami and cerebellum (Figure 3).

Complete blood counts were normal except for low platelet counts while bone marrow and bone histology revealed decreased numbers of erythrocyte precursors, megakaryocytes, and osteoclasts. Serology for TORCHS and chromosomal analysis revealed normal findings.

Despite ventilation with 100% oxygen, the baby developed progressive hypoxia and hypercarbia, and expired 36 hours later. Consent for autopsy was not granted.

Discussion

Various reports suggest that the malignant variant of osteopetrosis is relatively common in Saudi Arabia [8-11], and this has been attributed to the high rate of consanguineous marriages [11]. Both of our patients were products of consanguineous marriages, but neither families were close relatives nor belonged to the same tribe. Both patients presented at KKUH within six months of each other; this may be a coincidence, but may also indicate that malignant osteopetrosis is not uncommonly associated with bilateral choanal atresia in the environment. It has been shown that infants who develop malignant osteopetrosis demonstrate small cranial canals, small orbits and small nasoethmoid complexes but without significant bone thickening at an earlier stage [4]. Subsequent thickening of the skull leads to encroachment on related structures resulting in proptosis, blindness, deafness and various cranial nerve palsies. Involvement of a small nasoethmoid complex in such bone thickening may possibly result in bilateral choanal atresia thereby explaining the co-occurrence of malignant infantile osteopetrosis and choanal atresia.

Whether the occurrence of choanal atresia and malignant infantile osteopetrosis are truly common will be determined by findings in future studies. Pending the results of such studies however, we opine that radiographic screening for osteopetrosis is advisable whenever a neonate presents with choanal atresia. Infants with clinical features such as proptosis, hepatosplenomegaly, evidence of bone marrow dysfunction or family history of osteopetrosis should be screened for the disease. Such radiographic screening may also reveal intracranial calcifications which are also sometimes present in malignant osteopetrosis, as evident in one of our cases.

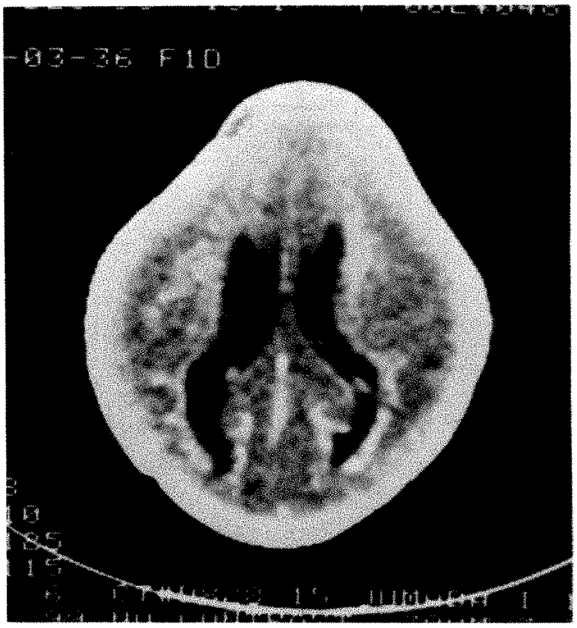

FIGURE 3. CT (brain) showing extensive intracranial calcification.

Bilateral congenital choanal atresia may cause respiratory embarassment including cyclical cyanosis in the immediate neonatal period, but this is easy to manage once a diagnosis has been made [7]. The complications of malignant osteopetrosis, particularly those related to bone marrow dysfunction, are more difficult to manage, and may result in death in early infancy from anemia, hemorrhages and overwhelming infections [3,12]. Pancytopenia is usual, but a leukemoid reaction, as was observed in one of our two patients, may occur and lead to an erroneous diagnosis of leukemia [12]. It is now possible to effectively treat some cases of malignant osteopetrosis with bone marrow transplantation [13], although facilities for this are currently limited to a few specialized centers. Treatment with steroids or high-dose calcitriol offers a potentially effective alternative treatment to bone marrow transplantation [14,15]. Very severely affected cases may manifest *in utero* and die prior to term as occurred in the cases reported by El Khazen et al [16]. Future developments may make treatment of such cases with *in utero* bone marrow transplantation feasible.

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SALMONELLA HADAR PERICARDITIS

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Acute purulent pericarditis is an infrequent but potentially life-threatening disease. Early and effective treatment requires a knowledge not only of the clinical course but also of the organisms commonly responsible. However, unusual microbes may be incriminated in immunocompromised hosts. We report a case of *Salmonella hadar* pericarditis in a female with systemic lupus erythematosus (SLE) being treated with oral steroids. Although other non-typhoidal Salmonella species have previously been implicated in the causation of bacterial pericarditis [1–9], infection of the pericardium with this species of Salmonella has not previously been reported.

Case Report

A 28-year-old female diagnosed to be suffering from systemic lupus erythematosus over six months preceding a current illness and maintained on prednisolone 10 mg daily was admitted to the Aga Khan University Hospital, Karachi, Pakistan, with a one-month history of low grade fever and progressive dyspnea on exertion leading to acute exacerbation of dyspnea over three hours prior to presentation. Systemic review was unremarkable. In particular, there was no history of fever, chest pain, cough or expectoration, bowel symptoms or recent procedures of any kind.

On examination, she was tachypneic with respiratory rate of 30 per min, and had a blood pressure of 100/90 mm Hg with a 10 mm drop in systolic pressure during inspiration. Her temperature was 39°C and a heart rate of 88 per minute. Pulse was of low volume. Internal jugular veins were distended to the angle of the jaw in sitting position and she had cushingoid facies. Apex beat was not palpable and heart sounds were reduced in intensity. There was no pericardial rub. Chest was clear on auscultation and liver span was 10 cm in the right mid-clavicular line. The remainder of the examination was unremarkable except for a malar rash and trace pedal edema.

Total leucocyte count was 10.9 × 10^9/L with 84% polymorphonuclear leukocytes. Erythrocyte sedimentation rate was 63 mm in the first hour by Westergren method. ECG showed low voltage and sinus tachycardia. Chest x-ray showed an enlarged cardiac silhouette. Echocardiography revealed massive pericardial effusion. Pericardiocentesis was performed and 1200 ml of thick purulent fluid was removed. On analysis, this pericardial fluid was exudative with a total leucocyte count of 59,000/ml of which 85% were polymorphonuclear leukocytes. Gram-stain revealed gram negative bacilli. The fluid was cultured on blood agar, chocolate agar, and Mac Conkey agar and incubated aerobically and anaerobically.

Salmonella species was isolated from this pericardial fluid and later sent to the Central Public Health Laboratory in Collindale, London, England, where it was typed as *Salmonella hadar phage type 2* which belongs to the non-typhoidal salmonella group C_2. Blood, collected prior to antibiotic therapy, was culture-negative following incubation of seven days. A stool specimen was also cultured and was found to be negative for any Salmonella species. However, antibiotics had been started prior to the collection of the stool specimen. Another stool specimen, collected

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after the resolution of the pericarditis also did not grow any organism.

The patient was initially administered ampicillin 1g intravenously every six hours and cefotaxime 1g every eight hours. After the identification of the organism and its *in vitro* sensitivity to both ampicillin and cefotaxime, ampicillin was withdrawn. Continuous drainage of the pericardial cavity was performed. Because of continuing hypotension, ampicillin (450 mg/kg/day) was reinstituted and cefotaxime was discontinued on the seventh day of hospitalization. There was good clinical response with only a small amount of pericardial effusion seen echocardiographically 14 days following hospitalization. The patient was discharged on the 18th post-admission day.

Discussion

The etiology of acute bacterial pericarditis is diverse [9]. Cardiac involvement with *Salmonella*, both typhoidal and non-typhoidal infection, has been recognized for many years. Myocarditis and endocarditis due to Salmonella typhi and other Salmonella species have been previously documented [10,11]. The first case of pericarditis in association with typhoid fever was described in 1844 by Volz [12], and reviewed by Levin and Hosier [13]. The first case of pericarditis due to non-typhoidal Salmonella infection was reported by Cohen et al in 1936 [14]. In 1986, Haggman et al summarized 23 cases of non-typhoidal Salmonella pericarditis reported since 1936 [15]. The most common species of Salmonella isolated was *S. typhimurium*. Two patients were found to have systemic lupus erythematosus but none had *Salmonella hadar* isolated from the pericardial cavity. This case report represents the first proven case of *Salmonella hadar* pericarditis.

Non-typhoidal serotypes of Salmonella are found in the intestinal flora from a wide range of animal species which are then transmitted from these animal reservoirs to humans primarily through foods of animal origin [16]. The reservoir of *S. hadar* in the United Kingdom has been identified in turkeys, although the organism has been isolated less frequently from chickens and occasionally from bovines [17]. In Pakistan, turkey is not a commonly eaten food, although chicken and other wild poultry birds may be the carriers of this organism in the country. The prevalence of *S. hadar* in the poultry flocks or bovine herds in Karachi, Pakistan remains unknown.

The pattern of infection characteristic of *S. hadar* in humans has until now been restricted to the abdomen, producing serious illness in elderly and debilitated patients. *S. hadar* has emerged as a common serotype isolated from patients suffering food poisoning in the United Kingdom [18].

It is difficult to determine the source and route of infection in our patient with pericarditis due to *S. hadar*. There was no history of food poisoning or gastrointestinal symptoms. Stool cultures were attempted after the organism was isolated from the pericardial fluid. However, possibly because of the patient's prior antibiotic therapy, the organism was not isolated. It can, nevertheless, be speculated that this patient may have acquired the species from water contaminated with poultry or bovine feces and carried in the gastrointestinal tract without any clinical manifestation. Because of the immunocompromised state, systemic spread occurred which manifested as massive pericardial effusion.

Acknowledgments

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SPLENIC SALVAGE IN HYDATID DISEASE

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Hydatid disease is one of the most common conditions in Saudi Arabia affecting mostly the liver [1]. Splenic hydatid cysts, on the other hand, are comparatively rare with splenectomy being the conventional treatment of choice [2]. The risks of splenectomy, especially the overwhelming post-splenectomy infection (OPSI), are well known [3], and although most commonly seen in infancy and early childhood, OPSI is not limited by age or underlying pathological conditions and remains a lifelong risk [4]. In obviation, alternative means of splenic preservation should be attempted whenever possible [3].

We present a case of hydatid disease of the liver and spleen treated by cyst enucleation and splenic salvage.

Case Report

A 38-year-old Saudi male patient was referred to the hospital with a history of abdominal pain and distention of ten years' duration. The patient had a laparotomy ten years prior to his presentation for ruptured hydatid cyst following trauma. The details of the previous surgical procedure were not available. On examination, the patient was found to be a healthy looking, thinly built male who was not pale or jaundiced. Abdominal examination revealed a midline scar, hepatomegaly was 5 fingers below the costal margin and splenomegaly, 6 fingers below the costal margin. Ultrasound examination of the abdomen showed two large cysts in the left lobe of the liver anteriorly and a cyst in the posterior aspect of the right lobe of the liver. There was also another large cyst in the spleen. Computerized tomography (CT) scan of the abdomen confirmed the ultrasound findings. The large cyst in the spleen was found occupying almost the whole of the spleen apart from a rim of splenic tissue (Figure 1).

At laparotomy, a large cyst was noted in the spleen. The spleen was mobilized and delivered into the wound and the other viscera were isolated by covering them with sponges soaked in hypertonic saline. Needle aspiration of the cyst revealed clear hydatid fluid. The fibrous capsule on the lateral surface of the spleen was incised and the laminated membrane was enucleated. Partial excision of the fibrous capsule on the lateral surface of the spleen was carried out. To restore the contour of the spleen, several stitches were inserted in the anterior edges to help obliterate the dead space. The cyst in the left lobe of the liver was totally excised while the cyst in the right lobe of the liver was enucleated and marsupialization of the cavity performed.

The postoperative recovery was uneventful. The patient was treated with albandazole for a

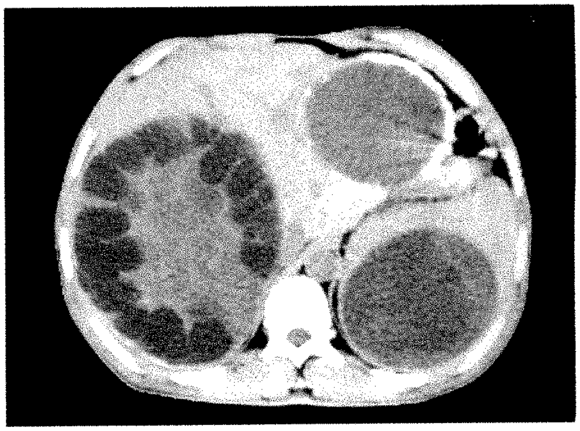

FIGURE 1. CT scan of the abdomen demonstrating two cysts in the liver and another cyst in the spleen. The cyst in the right lobe of liver shows daughter cysts.

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period of six weeks and CT scan of the abdomen performed 1½-years postoperatively (Figure 2) demonstrated an intact spleen.

Discussion

Cystic lesions of the spleen remain uncommon and are differentiated as two types: parasitic and non-parasitic cysts. The most common parasitic cyst of the spleen is the hydatid cyst caused by Echinococcus granulosa which accounts for more than two-thirds of splenic cysts. The splenic hydatid cyst usually presents as an asymptomatic mass which may grow into a large size, but which may also result in pressure symptoms or become complicated by infection or rupture.

In 1952, King and Shumaker [5] documented the association between splenectomy and OPSI in five infants undergoing splenectomy for congenital hemolytic anemia. Although OPSI was first documented in children, later reports also indicated its occurrence in adults [4]. In obviating the dangers inherent in total splenectomy and due to improvements in surgical techniques in recent years, alternatives to total splenectomy have become more feasible [3]. As postsplenectomy sepsis is most commonly seen in infancy and early childhood, elective splenectomy should be postponed until after the age of four years, if possible. The incidence of overwhelming sepsis following trauma is apparently low when compared with that following splenectomy for other disorders, but the consequences are no less serious. In order to reduce or eliminate complications, a number of measures have been employed which include non-surgical management in carefully selected patients provided that facilities for careful observation and follow-up are available, primary splenic repair, partial splenectomy, autotransplantation of portions of the spleen and ligation of the main splenic artery or primary divisions [3,6]. Splenic salvage maneuvers have already been used successfully in cases involving splenic trauma [6], splenic cysts [7], Hodgkin disease [8], thalassemia major [9,10], and Gaucher disease [11]. If splenectomy is unavoidable or indicated for underlying disease, routine vaccination and/or long term antibiotic therapy may confer partial protection. This is especially so in young children who are at a higher risk [12,13].

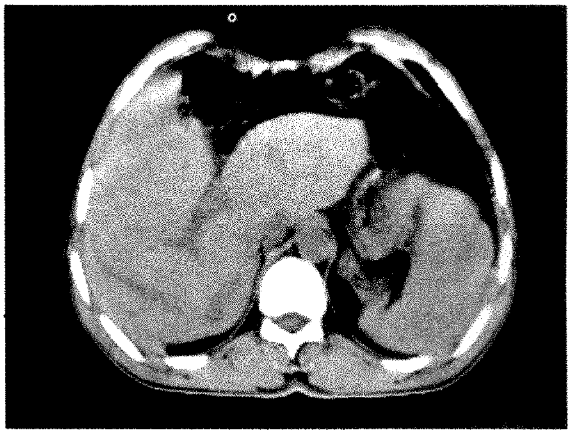

FIGURE 2. CT scan of trhe abdomen 1½-years postoperatively shows an intact spleen.

The primary treatment of hydatid disease anywhere in the body has been surgical and splenectomy remains the standard treatment for hydatid cysts of the spleen [2,14], but recognition of the dangers inherent in total splenectomy makes it possible to allow for alternatives to splenectomy. Cyst enucleation is a technically feasible procedure and is recommended in cases of hydatid cyst of the spleen [15]. Our case clearly demonstrates that splenectomy should not be the only standard treatment for hydatid disease, and in selected cases, it is possible to preserve the spleen. Although ultrasound has proved to be useful in the diagnosis of hydatid disease, we found CT scan of the abdomen (Figure 1) more valuable preoperatively because it provides valuable information on cyst size, site and the amount of unaffected splenic tissue.

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Neurologic Disorders in Saudi Children

To the Editor: Izuora and Anis reported a survey of neurological disorders in children from Asir province [1]. In addition to the limitations, the authors admit—partly retrospective small numbers—the study is hospital rather than population-based, and presents a prevalence, but not incidence figures, as have other reports [2–6]. Only one prevalence study of neurological diseases in Saudi Arabia has been population-based [7].

Nevertheless, I agree with the authors that the study is valuable in that the major neurological disorders in children which emerge are in concordance with experiences noted elsewhere in the world. The "big 3" in pediatric neurology in developed countries—epilepsy, cerebral palsy (CP), and mental retardation (MR)—also emerge as the "big 3" in Asir. It is surprising to note the relatively low level of infection and trauma considering the high rate of road traffic accidents and head injuries [8].

Compared to our experience at King Faisal Specialist Hospital and Research Centre, a tertiary care center, the prevalence of degenerative diseases seems low. We find that the initial presentation of many neurometabolic diseases including treatable ones such as aminoacidurias and organic acidurias, is that of CP and/or MR. It may be that such cases are hidden within these diagnostic categories in the authors' series. In patients who are labeled CP or MR, when there is no obvious perinatal etiology, and particularly when there is a family history of a similar case, the patients should be screened for neurogenetic or neurometabolic disease.

Every secondary hospital in the Kingdom should have the capability of performing a battery of simple, inexpensive reagent screening tests such as ferric chloride for aminoacidurias, DNPH (dinitrophenyl hydrazine) for organic acidurias, reducing substance, sodium cyanide-nitroprusside for homocystinuria, and a test for mucopolysaccharidoses. In addition, blood pH, lactate and ammonia levels would screen for organic acidurias that present with or without metabolic acidotic crises.

Our pediatric neurology patient data base reveals that 259 of 1,496 patients (17.3%) presented with seizures or epilepsy. These did not include those who also had MR or CP as a major diagnosis in which epilepsy coexisted. Izuora and Anis [1] listed 12 CP patients (35.3%) as having convulsions. These seem to be in addition to the 52 children they reported under the section of "convulsive disorders". This implies that the fraction of children with neurologic disorders who had seizures and epilepsy was even higher than the 28.9% they reported.

Since the only antiepileptic drug (AED) mentioned is phenobarbital because of its wide availability, it would be informative to know how many of the authors' patients with recurrent afebrile seizures (epilepsy) regardless of whether they were part of a cerebral palsy or mental retardation syndrome, or stood alone, were satisfactorily controlled at the primary care level, and did not have to be referred to a specialists' care by neurologists and neuropediatricians. This information would reinforce the authors' recommendation that hospital pharmacies at the primary, and certainly secondary care level, should stock AEDs, particularly carbamazepine, the drug of choice for partial epilepsy; valproic acid, the drug of choice for primary generalized epilepsy; and even rectal diazepam, for aborting status epilepticus at home. This information would also influence recommendations as to whether the ability to measure serum AED levels should be routine at secondary hospitals. It is widely accepted in the developed world that 80% of epilepsies can be managed by primary care physicians and AED monitoring is essential for modern care of epilepsy. Finally, it would be informative to know how many patients were treated unsuccessfully with cautery, herbal medicines, or other traditional treatments, and what was the time lag, before presenting to a primary health care center or regional hospital. This information would have implications regarding the need for public education in rural areas regarding epilepsy.

In summary, I agree with the authors' last recommendation that rehabilitation facilities, including provisions for the education of children with neurologic handicaps that prevent them from attending ordinary public schools, are sorely needed in the Kingdom's rural areas [9].

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Reply

To the Editor: We wish to thank Dr. Gascon for his interest and comments on our paper entitled "Neurological disorders in Saudi children in Al-Majardah General Hospital, Asir Region". Some limitations of the paper were clearly stated and at the time the study was planned, the issue of a community-based project was not feasible for various reasons. This not withstanding, hospital-based studies are often barometers to what occurs in the community.

Regarding the issue of low prevalence of central nervous system (CNS) infections; we were also surprised at our results. Unlike children with head injuries due to road traffic accidents who are often referred outright from the Emergency Room (ER) to tertiary centers without proper hospital documentation, our search for CNS infections (both prospective and retrospective) was comprehensive. As was stated in our paper, the excellent immunization status of of Saudi children in the locality and the well supervised primary health centers could have had some positive part to play.

Admittedly, cases of degenerative diseases might have been under-represented in our series. It is not unlikely that some of the children with idiopathic cerebral palsy and mental retardation might have been grouped under the category of degenerative diseases after adequate neurometabolic screening. On this issue, we are frankly not in a position to make any comments on constraints and limitations in the area of "research" at General/Secondary hospitals in rural areas and the poor feedback from tertiary health care centers.

As has correctly been observed, more than 52 (28.9%) children in the series had seizures; since 12 children with cerebral palsy were also treated for seizure disorders, giving a total of 64 (35.6%) – a high prevalence indeed! Since anti-epileptic drugs (AED) were not available at the Primary Health Centers, it is doubtful whether any of these children could be said to have been successfully treated at the primary level.

With phenobarbitone as the most available and consequently most widely used antiepileptic drug in the hospital, only about 18% of the children could be said to have responded satisfactorily to therapy. In addition to the fact that phenobarbitone is not the only drug of choice for generalized and not to mention for partial seizures, other factors which contributed to the low success rate included late presentation for treatment, poor compliance due to ignorance, irregular clinic attendance, and other socioeconomic factors.

As previously stated, we totally agree with Dr. Gascon that is feasible and logical that some major AEDs should be adequately stocked at general hospitals. Injectable diazepam and diazepam suppositories or rectioles should be made available at primary health centers to abort acute and prolonged seizures [1]. It also follows that measurement of AED levels should be monitored routinely at general hospitals because the machines for the tests are invariably available. What remains, however, is the appropriate utilization of staff.

Finally, that cautery, scarification, herbal medicines and other traditional forms of therapy are ineffective in the control of seizures cannot be overemphasized [2–4]. One may conclude that well-oriented health care education and regular appraisal of health care services are inevitable for all developed as well as emerging countries of the world.

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Traditional Healing Methods Prevalent in Zulfi Area

To the Editor: We read with interest the article entitled "Native manual tonsillectomy: a dangerous practice in Asir" by Awad et al [1]. This prompted us to share our experience about traditional healing methods prevalent in this area. Such practices create a lot of difficulties in the management of patients with, at times, dangerous complications and outcomes. The following are the most commonly practiced traditional healing methods in the Zulfi area:

(1) Sugat (سقاط). In this condition, parents present the child with complaints of sore throat, vomiting and depressed anterior fontanelle. Clinically, these patients are suffering from upper respiratory tract infection (URTI) accompanied by vomiting and dehydration. A local healer's method of management is: (a) Thorough massage of the tonsillar area with finger impregnated with salt water accompanied by upward pressure in an attempt at lifting the depressed anterior fontanelle from inside; and (b) Herbal paste is applied (contents unknown to us) over the anterior fontanelle and becomes very hard on exposure. This very sticky herbal paste .remains over the anterior fontanelle for several days and is very difficult to remove.

Case 1

A six-month-old Saudi male was admitted with a case of acute gastroenteritis with secondary lactose intolerance. The patient was managed by intravenous (IV) fluids and lactose-free diet. On the second day of admission, the parents took the child against medical advice to a local healer who then treated him as Sugat. The parents later returned the child to the hospital. While in the hospital the patient's mother refused all medical management. Later when the child became severely dehydrated, we were able, with great difficulty, to convince the mother to permit us to start IV therapy. The child subsequently improved and was discharged home in good condition.

2. Kowie (Skin cautery, كـوي): This is one of the most commonly used methods practiced in the Zulfi area for a variety of ailments ranging from simple abdominal colic in newborns to severe

infections in older children. The most common sites of cauterization are: abdomen, chest, midline of back, behind ears, limbs, and rarely over the anterior fontanelle. This method is usually performed by using a red hot iron bar (in small infants, the healer may use small pieces of burning wood). The iron bar comes in different shapes e.g., round, linear, crossed-shaped, etc. It is not surprising, even in this modern medical era, to notice a child with more than 50 cauterization marks.

3. Massae (مصع): These patients are taken to local healers with suspected trauma to the chest which is accompanied by pain. Clinically these patients are often suffering from lobar pneumonia. Local healers manage these patients by holding them by the wrists and hanging them in the air for a few minutes. The local healer then applies a large amount of sticky plaster tightly over the entire chest which is left on for several weeks and strictly advises the parents to maintain the child in a specific position.

Case 2

An 8-month-old Saudi male was admitted with a case of bronchopneumonia accompanied by pyogenic meningitis. On the second day of admission, the parents took the child against medical advice to a local healer who treated him as a case of Massae. The parents later returned the child to the hospital for further medical care. Due to thick sticky plaster covering the entire chest and positioning of the child strictly advised by the local healer, the mother created a great amount of inconvenience to us every day during examination of the child and during procedures e.g., lumbar puncture and x-rays, etc.

4. Traditional treatment for hepatitis: This condition is usually managed by multiple cauterizations primarily located over limbs and liver area in conjunction with herbal medications.

Case 3

A 4½-year-old Saudi female was admitted with a case of viral hepatitis. On admission, the child was highly febrile, toxic, deeply jaundiced and dehydrated. Liver function studies were markedly deranged. The child was managed as a case of impending hepatic failure. On the third day following admission there was little improvement in the child's conditon. Therefore, the parents took the child against medical advice to a local healer who promised an immediate cure. This child was later lost to follow-up.

In contrast to a previous study [1], local healers in our area are usually experienced elderly women. In our experience, we found that most of the parents, irrespective of their educational background, believed in these practices. As noted from the above mentioned cases, such practices create many difficulties in the proper management of patients, as parents usually demand the continuation of traditional treatment in addition to medical management. At times, it is impossible to convince parents not to follow these practices; however, every day many children are exposed to these unscientific, sometimes dangerous practices. It is our belief, apart from the above mentioned practices, that many other traditional healing methods are presently being practiced in the Kingdom of Saudi Arabia, which needs further exploration. We recommend that serious measures be taken by health authorities in educating people regarding proper health care awareness.

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Clinical Effect of Somatostatin Analogue (Sandostatin) In Three Cases of Non-Malignant Enteropancreatic Disorders

To the Editor: We report three cases of different non-malignant gastrointestinal disorders in which long acting somatostatin analogue (Sandostatin) was successfully used.

Case 1

A 39-year-old male technician was diagnosed and treated six months earlier in another hospital as chronic myeloid leukemia. He presented to us with an eight-week history of persistent diarrhea which was very watery and contained mucus and blood with a frequency of 20 motions/day. Investigations showed Hb 10.8 g/dl, WBC 12.1 × 10^{12}/L, platelets 64 × 10^9/L, ESR 1 mm/hr, urea 4.1 mmol/L, Na 135, K 3.2 mmol/L and creatinine 68 μmol/L. Repeated stool examination showed no ova or parasites and culture was sterile. Serology tests for salmonella, ameba, schistosoma, brucella and legionella were all negative. Tuberculin skin test was negative, viral screen showed him to be immune to hepatitis B virus and negative for anti HCV and HIV. Sigmoidoscopy showed extensive mucosal ulcerations throughout the sigmoid and descending colon. Mucosal biopsy was consistent with acute non-specific colitis. Gastroscopy showed antral erosions with multiple duodenal ulcerations. Duodenal mucosal biopsy showed inclusion bodies typical of CMV in epithelial cells. Famotidine 40 mg od and acyclovir 400 mg orally five times a day were prescribed together with lopramide and diphenoxylate. The patient was commenced on TPN (Total Parentral Nutrition). Although his body weight remained steady, his diarrhea persisted. Oral antidiarrheals were discontinued and sandostatin 50 mg subcutaneously once a day was commenced. This was gradually increased to 50 micrograms twice daily and only when was some improvement in the patient's condition observed. When the diarrhea became better, TPN was discontinued and the patient was permitted to take sandostatin orally. Sandostatin was carried out at the same dose. After a two-week period of treatment with sandostatin, repeat sigmoidoscopy examination showed healing of the previously seen mucosal ulcerations. Also, a repeat gastroscopy reported healing of the upper GI ulcerations, and biopsy showed the disappearance of CMV particles. The patient gained weight and his general condition improved markedly. Prior to discharge from the hospital, both acyclovir and sandostatin were discontinued. Follow-up in the outpatient department on two subsequent visits were satifactory.

Case 2

A 24-year-old Saudi female with a known case of Crohn disease was readmitted to the hospital because of copious discharge from enterocutaneous fistulae. Seven years ago she had a right hemicolectomy and again had surgery four years later for fistula excision. However, since then she had been in and out of the hospital with worsening episodes of her fistulous disease. The patient was maintained on prednisolone 10 mg od and sulphasalazine 1 g qid. Full blood count and chemical profile were unremarkable. Swabs from the fistula discharge grew multiple cliform organisms and heavy growth of E coli and Klebsiella species. The patient was commenced on TPN and kept on her regular medication of salazopyrine 1 gm qds, prednisolone 40 mg daily in addition to famotidine 40 mg daily. Appropriate antibiotics were added as per the sensitivity report. No substantial reduction in the amount of discharge or healing of the fistulae was noted and hence a dose of 50 mcg subcutaneously daily sandostatin was added which was gradually increased later to 50 mcg three times a day. The discharge gradually decreased and the fistulae began to close after the first week of treatment. TPN was discontinued and the patient was discharged home on reduced prednisolone 15 mg/d to be followed up in the outpatient department. On subsequent visits to the outpatient department the patient continued to improve with no further recurrence of fistulae while still being maintained on the same dose of sandostatin 50 mcg/day.

Case 3

A 65-year-old female with gallstone disease was admitted for ERCP. Twenty-four hours later she experienced severe localized epigastric pain which was partially relieved in the sitting position. She had repeated vomiting but no change in bowel habits. Abdominal examination showed marked tenderness both in the epigastric and right hypochondrial regions. The impression was that of acute pancreatitis most probably following ERCP. Abdominal ultrasound showed no obvious pancreatic abnormality. Serum amylase was 2050 iu/L. She was kept on NPO and IV fluids. To relieve her symptoms, sandostatin at a dose of 50 mg subcutaneously three times a day was commenced. The patient's symptoms began improving soon after the initiation of sandostatin and by the following day was completely symptom-free and serum amylase dropped to 900 iu/L. Sandostatin was discontinued and the patient was discharged home on the third day. Two weeks later she was followed up in the outpatient department where her condition was noted to be quite stable.

Comments

Somatostatin, a tetradecapeptide, has a wide range of inhibitory properties which include: (1) different body systems, particularly the gastrointestinal tract; (2) its use in malignant conditions with high production of intestinal peptides has been well established; (3) however, through the mechanism of blocking hormone receptors, somatostatin decreases secretory output as well as prolongs the intestinal transit time; (4) water and electrolyte absorption is enhanced. Thus, at least in theory, it should have an effect in cases involving intractable diarrhea of unknown origin and in those with excessive pancreatic exocrine secretions; and (5) in Case 1, sandostatin may have had a role in the marked improvement in the endoscopic picture as this agent has been known to have an ulcer-healing effect. The time taken for a fistula to heal may be months, but in Case 2, it took only a couple of weeks. Although acute pancreatitis complicating ERCP is a self-limiting condition, we believe that sandostatin treatment alleviates symptoms much quicker and hence, minimizes the patient's suffering. In conclusion, we believe that there is a case for using somatostatin analogue as a symptomatic treatment in certain gastrointestinal disorders whereby no other specific curative therapeutic modality may be offered.

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Presumptive Tuberculosis of the Esophagus

To the Editor: I read with some unease the report of Kagevi et al [1] "Presumptive tuberculosis of the esophagus". The fact that the authors were unable to isolate the mycobacteria which is crucial for the diagnosis of any tuberculous infection, makes the diagnosis rather weak or questionable. The absence of lymph node tuberculosis (TB) as the most frequent cause of extrapulmonary TB [2] and the exclusion of a pre-existing esophageal disorder which would have facilitated the mycobacterial inoculation makes it difficult to accept the diagnosis. Although the histopathology was compatible with a mycobacterial infection, other bacterial, viral, or traumatic etiologies which could have presented a similar picture were not excluded [3,4]. The clear improvement on the short course of ranitidine used may favor other etiolgies.

More than 50 cases of esophageal tuberculosis have been previously reported in the literature, but only nine, to my knowledge, were described as primary TB [5].

I concur with Kagevi et al that the diagnosis of primary esophageal tuberculosis is difficult to prove. Even in the few reported cases, the absence of tuberculosis in other sites has not been fully documented and in others was not carefully investigated, making this diagnosis difficult to accept [6]. The positivity of purified protein derivative (PPD) test should always be interpreted with caution as it once meant nothing more than the reality that the patient had been infected in the past and continued to carry mycobacteria. The response to antituberculums used, although solely not diagnostic, should be considered. However, rifampicin has been known to have a broad spectrum of activity.

I believe more data are needed to define risk factors, course of the disease and more importantly, the diagnosis of primary esophageal tuberculosis in the absence of mycobacterial isolation.

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Reply

To the Editor: With reference to the letter from Dr. Elsheikh, this diagnosis is usually difficult to prove except when mycobacteria are isolated from the lesion. However, endoscopic biopsies from the gastrointestinal tract rarely reveal mycobacteria in cases of gastrointestinal tuberculosis [1–4]. Elsheikh also points out the "improvement" of the esophageal lesion in our case on a short course of ranitidine. As mentioned in our article, this could be explained objectively by inter-observer variation and subjectively from the patient's point of view as a placebo effect from the drug and its reassurance.

It is very unlikely that other microorganisms could have caused the lesion, presenting in this fashion and requiring such long treatment before healing, in an immunocompetent person.

It is possible that the patient's esophageal lesion could have been secondary to an adjacent mediastinal lymph node undetected by the computed tomographic (CT) examination of the chest. Whether this lesion was truly primary in the esophagus or secondary to a mediastinal lymph node was impossible to ascertain.

However, tuberculosis remains the most probable cause of the lesion that responded gradually but completely to the one-year course of antituberculous therapy.

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The Risk of Heat Illness in Children Administered Antihistamines During Heat Acclimatization

To the Editor: Heat acclimatization is primarily due to an increased efficiency of the sweating mechanism; a decrease in the sweating threshold combined with an increased sensitivity per unit change in the sweat drive results in the production of more sweat for a given increase in the core temperature [1]. Antihistamines suppress sweating and increase the risk of environmental heat injury [2]. Four children aged 4–6 (mean 4.8) years with fever were observed in Northern Cyprus last summer. All of the children (3 males, 1 female) arrived in Northern Cyprus from Turkey a few days earlier. Because of hyperactivity and/or sleeping disorders, the children were ingesting doses of diphenyhydramine 5 mg/kg/day prior to entering the island. On history, no additional problems other than psychosocial disorders were noted. Upon arrival to the island, the children continued to be administered diphenyhydramine and sustained fever continued to appear during this period. Rectal temperatures varied between 101.5°F and 102.6°F. All had fever which was characterized by persistent elevation without significant diurnal variation. Physical examination and routine laboratory tests were normal. Upon discontinuation of the antihistamine therapy, fever disappeared and a decrease in body weight, 200–300 gm, was found. However, body sweat rate could not be calculated by using a dew point sensor. Although additional side effects of antihistamines in children include dryness, rash, dizziness, hyperreflexia, tremors and convulsions, these symptoms were not found in our cases. In conclusion, we considered that there was a relation between fever and the antihistamine therapy administered to these patients.

Certain characteristics of children make them less efficient thermoregulators than adults, particularly when exposed to extreme weather conditions. Children have a lower rate of sweating due to the lower output of each sweat gland [1,3]. The aim of this letter is to emphasize that the use of antihistamines in children may be a cause of heat-related illness during hot weather conditions.

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Malignant Mesothelioma in Saudi Arabia

To the Editor: I read with great interest the article entitled "Malignant mesothelioma: King Faisal Specialist Hospital and Research Centre experience" by Khan et al [1] and would like to address several points:

Although I do not doubt the histological diagnosis of the ten cases described, the finding that only one case had established occupational exposure to asbestos is most likely explained by incomplete occupational and environmental histories. Most patients have had several occupations during their working lives and physicians tend only to record the last occupation. Retired people often give the most prestigious occupation when queried. It is also probable that the two Bedouins mentioned in the study had had several undisclosed occupations during their lives. In addition, the two housewives described in the study with mesothelioma, the occupations of their husbands are relevant but were not stated. Asbestos exposure has occurred when wives wash contaminated work clothing of their husbands.

Thus, the occupations stated in this study may be very misleading, this being particularly relevant when one considers the long dormant period (at times as long as 40 years) between the exposure to asbestos and the development of mesothelioma.

There was no report in the study denoting whether sputum or lung histological searches for asbestos bodies were performed which could have also established exposure to asbestos.

To my knowledge, asbestos is not presently being mined in Saudi Arabia but there have been vast amounts of imported insulating materials etc., pipes and automobile brake shoes; many of which contain asbestos. Demolition sites and junk yards are the most likely places for asbestos exposure.

Mesothelioma is a rare tumor and asbestos is the most common known cause. Although it is tempting to postulate other causes of mesothelioma, I believe the most likely cause of mesothelioma in the cases described in this study was asbestos exposure.

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Reply

To the Editor: We agree with Dr. JC Hughes that complete occupational histories are often not recorded; however, responsible information regarding our patients' occupations was available, some of which was recorded after the diagnosis had been established.

Since the publication of this article, two more cases of malignant mesothelioma have been diagnosed. A 40-year-old female was referred from the same area where other cases were identified. None of her household members were occupationally exposed to asbestos.

Light and electronmicroscopy did not reveal asbestos bodies in the histological material of these patients, including the one with possible exposure to asbestos. In fact, the search for asbestos bodies has been negative in over 4,000 sputum and lung tissue specimens examined during the past ten years.

We feel that the cause of mesothelioma in the Southern Region of the Kingdom remains unknown.

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Childhood Brucellosis: Experience in Tathleeth

To the Editor: Childhood brucellosis, once thought to be rare [1,2], has increasingly been reported from the mainly urban centers of Saudi Arabia [3–5]. Conversely, reports of its occurrence or its characteristics in the rural areas of the Kingdom have been relatively few.

During a period of 21 months, we managed 88 children with brucellosis at the General Hospital in Tathleeth, a small rural town with a population of about 10,000 people in the Asir region.

The diagnosis of brucellosis was based on a combination of clinical features and confirmatory titers of at least 1:320 *Brucella abortus (B. abortus)*and *Brucella melitensis (B. melitensis).* The brucella titers were determined by the agglutination method using a microtiter serial dilution standard technique.

The 88 children, 40 males and 48 females, were all Saudi nationals and age 10 months to 12 years (mean 7.3 years). Forty (45.5%) of the cases came from 16 families where between two and five children per family had brucellosis.

The majority of symptoms comprised intermittent fever (55%), joint pains (46%), leg pains (26%), headache (17%), inability to walk (13%), and generalized aches and pains (10%). It was interesting to note that 13 (15%) cases presented with recurrent fever as the only symptom, while ten (11.4%) cases had no symptoms, the diagnosis having been made on routine screening of the families in whom cases had been diagnosed. In 25 (28.4%) additional cases, the parents volunteered symptoms only after family screening revealed high brucella titers in the children. A positive history of habitual ingestion of raw goat's/camel's milk was obtained in 58% of cases. An interesting case was that of a 12-year-old girl who presented with fever, arthralgia, epistaxis, bleeding gums, a history of close and regular contact with livestock and that of regular ingestion of raw goat's milk. Investigations revealed thrombocytopenia (platelet count $< 10.0 \times 10^9$/L), a bone marrow picture which was compatible with that seen in idiopathic thrombocytopenic purpura and a brucella titer of 1:1280 to both *B. abortus* and *B. melitensis.* The symptoms subsided and the platelet count increased to 183×10^9/L six days after commencing antibrucella therapy when the brucella titer also decreased to 1:320.

Thirty-eight (43.2%) of the 88 cases including the ten with no symptoms were free of abnormal physical signs. Signs present in the remaining cases included pyrexia (52.3%), limitation of movement (17%), limping (10%), and tender joint swelling (8%). Although hepatosplenomegaly has been reported as being common in some series, this feature was distinctly uncommon in our cases; only three cases each had hepatosplenomegaly and splenomegaly. Of the 43 cases with joint involvement, single joints were involved in 28 cases and multiple in five, while the number was not recorded in ten cases.

Brucella titers ranged between 1:320 and 1:5120. Hematological data showed that only 10% of 52 cases had a hemoglobin of 100 gm/L. While the total white blood count was within normal limits in most cases, the lymphocyte proportion was > 40% in 87% of 53 cases. The erythrocyte sedimentation rate varied widely between 4 and 90 mm/h (mean 35.2); there was no relationship between the rate and the type of lesion.

Initial routine treatment consisted of daily oral rifampicin and cotrimoxazole from 12-18 weeks. Additional forms of therapy included paracetamol for fever and pain, and when required, bed rest and splinting of affected joints. Twenty-five (28.4%) of the 88 cases received inpatient treatment; they were mainly those with high fever, severe arthritis or those who were apparently not responding to treatment on an outpatient basis. Among those admitted were five cases who relapsed after adequate treatment, and two who defaulted while in therapy. Ten of 25 patients received intramuscular streptomycin in addition to oral therapy. The remaining 63 were treated throughout on an outpatient basis. Response to medical management was satisfactory. Fever usually subsided within seven days of treatment in those admitted with this feature. Symptoms of body ache and joint pain abated within one week and one month, respectively in most cases, while joint swelling usually subsided within 2–3 weeks.

Our findings suggest that the features of childhood brucellosis in this rural setting are similar to those reported from urban centers in the Kingdom [3,4] and elsewhere [2]. Nevertheless, an important aspect which appears not to have been adequately emphasized is the fact that some children with brucellosis remain asymptomatic or if symptomatic, are not identified until after routine family screening. This phenomenon indicates that the incidence of the disease has probably been underestimated and will continue to be so unless at-risk populations are screened. Another aspect is whether or not to treat asymptomatic cases. Our practice has been to regard such patients as suffering from brucellosis and offer drug therapy. It is hoped that such treatment will prevent neurological involvement. An area of some controversy concerns the duration of drug treatment in cases of childhood brucellosis. Based on our experience, we believe that provided there is patient compliance, a three-month therapy with rifampicin and cotrimoxazole will suffice in the vast majority of cases.

We are aware of plans to eradicate brucellosis from the Kingdom. However, for some time to come, there will continue to be clinical and subclinical cases of childhood brucellosis, particularly in rural areas where the risk factors such as close contact with dairy animals and the practice of drinking raw milk remain high. It is, therefore, important that measures be designed to reduce the local incidence and to provide optimum treatment to identified cases. In this connection, the importance of educating parents on the need to boil noncommercially prepared milk before drinking or using it in preparing products such as cheese and of not eating meat in an uncooked state needs to be stressed. Parents also need to be assured that the disease is curable, provided there is compliance with regular drug therapy in addition to adequate follow-up of cases with monitoring of titer levels which, though imperfect for the purpose, may give some indication of when to discontinue therapy. This is to avoid having to give unnecessary prolonged high cost treatment with the possible side effects of potent drugs used.

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Cutaneous Leishmaniasis in Majardah (Asir Region), Southern Saudi Arabia

To the Editor: I read with interest the letter from Dr. Malik [1] on the epidemiological studies of cutaneous leishmaniasis at Leishmania Center Abha, and add the following comments:

A study of only 34 cases of cutaneous leishmaniasis is not a large enough number to infer a concrete conclusion regarding the incidence and other causative epidemiological factors and immunological susceptibility of the population for the development of cutaneous leishmaniasis.

As the author has hypothesized that children younger than the age of five years are not exposed to sandfly bites, thus making the incidence less in this age group (0–5 yrs). But in a study of 15 cases of cutaneous leishmaniasis attending the skin outpatient department (OPD) of Majardah General Hospital during the period of one month, ten (66%) cases were children younger than 13 years of age. Of these, one case was 1 yr/7 months and another 1 yr/3 months of age.

The subject of cutaneous leishmaniasis has been extensively reported from Saudi Arabia [2]. Levamisole, an immunostimulant drug, has been recognized as a standard method of treatment in resistant cases of cutaneous leishmaniasis [3], and has a stimulating effect on cellular immune mechanism.

Therefore it can be assumed that children are more prone to developing cutaneous leishmaniasis due to the lack of a fully developed cellular immune system, although no age is resistant to this form of cutaneous disorder.

Extensive prophylactic measures are required to protect children from sandfly bites as well as the discovery of modern immunological methods which should be discovered and utilized to boost the cellular immunity of children to minimize the incidence of cutaneous leishmaniasis.

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Management of Diabetic Foot Lesions With Limited Use of Antibiotics

To the Editor: The magnitude of foot lesion problems is illustrated by the observation that the prevalence of gangrene is 53 times higher in diabetic males and 71 times higher in diabetic females than in nondiabetic males and females, respectively [1].

To date, there is no evidence that antibiotics alone, either topically or systemically, can ready a chronically contaminated wound for healing [2]. Wound healing can be potentiated and accelerated by reduction of bacterial contamination. Thus, reduction of bacterial numbers must depend primarily on vigorous local care of the wound and treatment of diabetes.

The present study was conducted to assess the efficacy of bland vigorous local drainage and debridement of the lesion versus additional use of local antiseptics with limited usage of antibiotics in either condition.

From August 1990 to January 1991, 30 diabetic cases with foot lesions were prospectively studied in the surgical department in King Fahad Hofuf Hospital. The patients were randomly allocated into three groups, ten cases per group. Group I lesions were dressed with 1% aqueous chlorhexidin; Group II was dressed with 0.25% acetic acid; and Group III lesions were dressed with normal saline two to three times per day, for mechanical removal of bacteria from the lesion.

Each patient was subjected to a thorough history taking, clinical examination, assessment of the limb arterial blood flow by palpation and/or doppler, routine laboratory investigations, blood and urine cultures, x-ray of foot and fundoscopy. From every wound, three swabs were obtained for culture and sensitivity test; from the surface, subcutaneous space and the depth of the lesion, on admission and on a weekly basis. Each case was submitted to release incision and generous debridement of necrotic tissue and excision of gangrenous toes when needed. Unless there was a temperature over 37.5°C, cellulitis, positive blood culture and/or urine culture, no antibiotics were prescribed.

Optimal control of diabetes was effected through appropriate adjustments in insulin doses.

The patient was considered recovered when his blood sugar was below 8 mmol/L, his wound ceased discharge, swab culture became negative and wound became nicely granulated with progressive epithelialization. Thereafter, the patient could be discharged to continue dressing on an outpatient basis if required.

The overall mean age of the studied cases was 54.5 years. Eight cases (26.7%) were insulin dependent; three cases in Groups I and II, two cases in Group III, and 22 cases (73.3%) were non-insulin dependent diabetics. The overall mean duration of the disease was 11.4 years.

The prevailing lesion in the present study was foot ulcer in 18 cases (60%) as shown in Table 1. The overall mean blood sugar level on admission was 24 mmol/L. Serum creatinine was elevated in two cases, one in each of Groups II and III. Posterior tibial and dorsalis pedis pulsation was undetectable in 11 out of the 30 cases (36.7%). All the amputated cases were from these cases. Three cases presented with septicemia, one in each group, and had positive blood cultures. Urine culture was positive in five cases, of which two had positive blood culture as well. They received antibiotics according to the sensitivity test. This means that antibiotics were used in six cases, two in Group I, three in Group II, and one in Group III.

The most common organisms isolated from the studied cases were *Klebsiella* in 28 swabs, *Streptococcus fecalis* in 22 swabs, *Proteus* in 18 swabs and *Pseudomonas* in 17 swabs, respectively. The number of positive deep swabs for these organisms were more than those of subcutaneous and surface ones. Nine swabs were negative; five surface, three subcutaneous, and one deep, respectively.

TABLE 1. *Presentation of foot lesions.*

	Group				
Lesion	I	II	III	Total	(%)
Ulcer					
Alone	3	5	4	18	60
With cellulitis	2	1	3		
Abscess	4	3	1	8	26.7
Gangrene of toes					
Alone	1	–	–		
With cellulitis	–	1	2	4	13.3

Three cases (10%) underwent major amputation. One from Group II underwent below knee amputation and expired due to septicemia, ischemic heart disease, hypertension and chronic renal failure. The septicemia case of Group I underwent above knee amputation and expired due to uncontrollable septicemia. In Group III, one patient underwent below knee amputation due to rapid spread of tissue necrosis and ran an uneventful postoperative period and later on was able to touch the ground and walk with the help of a prosthesis.

A residual raw area was left in three cases, two in the plantar aspect and one in the lateral aspect of the foot extending into the leg. These patients were discharged to the plastic surgery ward where split thickness skin graft was performed.

Our philosophy in dealing with diabetic foot lesion is based on four facts. First, we are unable to totally improve peripheral neuropathy or peripheral vascular insufficiency [3]. Second, foot infections in diabetics are polymicrobial in etiology [4]. Third, the efficacy of systemic use of antibiotics depends in part on competent peripheral circulation [2], and Fourth, the high level of sugar in the tissue of uncontrolled diabetes makes this an excellent substrate for bacteria proliferation [5]. Therefore, we built up our strategy to enhance foot lesion healing on reducing the bacterial bulk in the foot lesion by using either topical antiseptics or mechanical wash with saline with very little use of antibiotics.

No significant difference was detected between local antiseptic use and saline wash in reducing the magnitude of bacterial load. This is evident in the progressive reduction of the number of positive swabs obtained from the depth of the lesion as surface swabs are unreliable whereas deep swabs provide more reliable results [4]. However, a larger number of cases should be studied before providing a solid document in favor of the mechanical method used in reducing bacterial bulk rather than the use of antiseptics or antibiotics.

We achieved a lower overall mean hospital stay (18 days) than that of the other study (6.8 weeks) [6]. This may be attributed to the lower frequency of major amputation (10%) and lower mortality rate (6.7%) documented in our study compared to 34.1% major amputation in the study conducted by Sulimani et al [6].

Additional hospital days are spent treating diabetic foot infections than are spent for any other complication of diabetes, resulting in enormous financial burden imposed on hospitals [1]. If we know that more than 80% of major amputations of the lower extremities occur in diabetic patients [7] and that 50% of these amputations are preventable [3] we can then realize that reduction of morbidity and hospital stay are achievable goals.

Despite the small number of the studied cases, the outcome of the regimen used in either group in terms of mortality rate, major amputation and mean hospital stay points out that the most effective weapons against diabetic foot lesions are the prompt active control of diabetes and aggressive persistent debridement. Moreover, patient education is the most influential factor in saving diabetic foot.

The story does not end by healing of the foot lesion because the risk of recurrence in a previously affected area remains three times higher [8]. Therefore, custom made shoes with orthoses should be prescribed to redistribute loads normally borne by the metatarsal area. Again, team treatment and good pedorthic management can prevent above or below knee amputations in complicated diabetic foot lesions.

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A Pilot Study of Associated Factors of Essential Hypertension in Saudi Residents of Almedina Almounawarah

To the Editor: Two mechanisms were thought to play a role in causing essential hypertension; a neurogenic origin and/or sodium mechanism. We report a population case control study of a number of factors associated with essential hypertension, including 24-hour urinary sodium, potassium, and sodium:potassium ratio; obesity (as Body Mass Index, BMI); family history of hypertension, exercise, and cigarette smoking. An also between population comparison of; 24-hour urinary sodium, potassium and sodium:potassium ratio was drawn between our findings and those from other countries as reported in the Intersalt study [1].

This study was conducted at the same time while studying the prevalence of hypertension in the Saudi population of Almedinah

Almounawarah; the results and reasons for studying the 50–60 year age group have been reported elsewhere [2]. A computer generated simple random sample including 50% of all the hypertensive subjects (cases) was compared to sex and age-matched normotensive subjects (controls). Hypertension was defined for this study as blood pressure of more than 149/90 and/or those on anti-hypertensive therapy. A structured questionnaire was applied by an interviewer to all subjects and which included the identity (name, age, address, telephone number); social history (marital status, job, smoking habits and exercise); and family history of hypertension. Subjects diagnosed as being hypertensive were questioned about a history of renal failure, unilateral renal disease or operations, drug history (anti-hypertensive; steroids) and whether or not they restricted their salt intake. An examination of all subjects included; weight and height (using a Stadiometer and a balance beam scale). Blood pressure (sitting) was measured twice using a standard mercury sphygmomanometer and the bell of a Littman stethoscope. Diastolic pressure was recorded when all sounds disappeared (phase V). Cases were screened clinically for features suggestive of secondary hypertension (cushingoid features, radiofemoral delay, enlarged kidneys and bruits of renal artery stenosis). Cases with signs suggestive of secondary hypertension were excluded. Hypertensives not restricting their salt intake nor on diuretics were directed to the laboratory. They were instructed on the method for collecting a 24-hour urine specimen and were asked to remain fasting the day the urine sample was returned to the laboratory, when a specimen of blood was collected for serum creatinine estimation. Completeness of urine collection was assessed at the time of delivery of the specimen by a standardized interview. On the day the specimen was received, the urine volume was noted and its content of sodium and potassium was established by photometry [3].

All data were handled by computer on Lotus and CIA software. To compare our results regarding urinary electrolyte excretion with those of the Intersalt study [1], a random sample of 100 subjects (50 males and 50 females) with ten hypertensives (three males and seven females) and the remaining normotensives had the variables of blood pressure fed into the computer along with similar variables from 52 centers reported in the Intersalt study. The variables included systolic BP, diastolic BP, prevalence of hypertension, 24-hour urinary sodium, potassium and sodium: potassium ratio.

The results of comparisons of key variables between cases of hypertension and normotensive controls are noted in Table 1. For male case-control mean (SD) age was 57.1 (3.4) and 56.5 (3.8) years; mean (SD) systolic BP 155.6 (24) and 119 (7.3) mmHg; mean (SD) diastolic BP 98.5 (15) and 76 (5) mmHg. For female case-control the corresponding values were as follows: 54.1 (3.5) and 54.5 (3.9) years; 160.5 (18) and 118 (8) mmHg; 97 (12) and 76 (5) mmHg, respectively.

Table 2 illustrates the comparisons of our results to that of the Intersalt study with the variables of blood pressure arranged in order of increasing 24-hour urinary sodium:potassium ratio. The correlation coefficient of mean systolic BP, mean diastolic BP and prevalence of BP to 24-hour urinary sodium:potassium ratio was 0.57, 0.42 and 0.94, respectively whereas the corresponding values for 24-hour sodium and 24-hour potassium were 0.07, 0.04, 0.06 and 0.07, 0.01, 0.01.

Of the associated factors we studied, only the family history of hypertension was reported significantly higher by cases, a finding reported by others [4], where normotensive blood relatives of hypertensive patients have a greater chance of developing elevated blood pressures. The within population comparison of urinary electrolyte excretion revealed no statistically significant difference. This within the community approach to studying the relation between salt and hypertension has its problems, as individual variation in blood pressure and salt intake is hardly controllable. Suggested solution was to average several measurements of blood pressure and salt intake or excretion [5]. Another approach to studying the relation of salt and hypertension is by analyzing mean BP and measuring sodium excretion across different countries [6], the largest study of this kind to date is the Intersalt study [1]. In this way our results fit nicely with those of the Intersalt study, where variables of blood pressure (mean systolic BP, mean diastolic BP and the prevalence of BP) correlated best with the 24-hour urinary sodium:potassium ratio.

In conclusion, our findings suggest the need for a large scale community-based study to look at probable genetic and/or environmental factors to explain the positive family history in Saudi patients with essential hypertension. Of the probable environmental factors, sodium intake and/or excretion deserves special attention.

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TABLE 1. *Case control comparison of factors associated with essential hypertension (Men* = 137, Women = 87).

Associated factor	Mean (SD) 24-hour urinary sodium (mmol/L)	Mean (SD) 24-hour urinary potassium (mmol/L)	Mean (SD) 24-hour urinary sodium: potassium ratio	Mean (SD) body mass index wt(kg)/ht(m^2)	Frequency of smokers	Frequency of positive family history of hypertension	Frequency of those on regular exercise
Cases							
Male (n = 49)	177.6 (94) [26]	66.7 (29) [26]	2.74 (1.14) [26]	24.3 (4) [48]	15/49	11/49	0/48
Female (n = 39)	122.6 (79) [24]	44.6 (22) [24]	2.71 (1.47) [24]	31.9 (6.6) [37]	00/39	8/39	00/39
Controls							
Male (n = 88)	195.5 (11) [60]	61.9 (30) [60]	3.3 (1.4) [60]	26.5 (5) [82]	32/88	5/88	5/88
Female (n = 48)	161.9 (60) [32]	54.7 (31) [32]	3.48 (1.59) [32]	30.2 (6.6) [48]	00/48	2/48	00/48
P-value							
Male	NS**	NS	NS	NS	NS	$.0027 < P < .02$	—
Female	NS**	NS	NS	NS	—	$.01 < P < .046$	—

*Cases: defined as BP > 140/90 and/or antihypertensive drug treatment. **NS: not significant.

TABLE 2. *Comparison of blood pressure variables arranged in order of increasing values of "24-hour sodium:potassium ratio as independent variable" (a comparison of Al-Medina Al-Munawarah (KSA) with Intersalt Study results).*

Country	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Prevalence of hypertension (%)	24-hour urinary sodium (mmol/L)	24-hour urinary potassium (mmol/L)	24-hours urinary sodium:potassium ratio
Italy (Naples)	112.4	72.9	13	162.6	59.5	2.78
Spain (Mantesa)	117.9	68	15.5	175.2	67.3	2.96
USA (Goodman-Whites)	115.6	72.4	19.7	125.9	43.1	3.16
Italy (Bassiano)	124.6	79.6	24.6	175.9	56.6	3.20
Italy (Gubbia)	118.1	69.9	16.2	169.9	54.2	3.23
USA (Hawaii)	123.7	72.3	23.3	130.3	39.8	3.29
KSA (Al-Medina, Al-Munawarah)	118.8	76.5	10.0	177.6	54.2	3.30
Mexico	110.9	72.6	5.9	134.6	39.9	3.31
Soviet Union	115	72	15.5	161.8	47.1	3.31
Canada (Labrador)	119	73	22.6	148.9	43.7	3.34
Canada (St. John's)	123.1	79.1	24.5	184.3	57.6	3.36
India (New Delhi)	110.9	73.9	13.6	153.2	46.3	3.37
Poland (Krakow)	120.5	75.7	19	191.8	50.5	3.71

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Neuroleptic Malignant Syndrome: Risk Factors!

To the Editor: McLean et al [1] have described neuroleptic malignant syndrome (NMS) in four patients in a comprehensive way. Despite the detailed presentation of NMS, the possible risk factors as revealed by these patients or reported elsewhere in the literature have not been highlighted or discussed in this interesting paper. Based on my experience with an unreported fatal case of NMS and detailed review of NMS literature, I would like to add some points which may be of considerable importance to clinicians.

NMS was first described in America (1959) and France (1960) and this term was coined in 1968 by Delay and Denikar especially in relation to the malignant hyperthermia which implies a body temperature of more than 40°C and induced by neuroleptics which have both antipsychotic and extrapyramidal actions. With the growing list of non-neuroleptic drugs causing neuroleptic malignant syndrome-like states and/or its atypical mild presentation for example; first, NMS induced by heroin and second, the average body temperature of all four patients was 37.7°C and moreover, notably case No. 3 was diagnosed with NMS despite having a low body temperature (35.9°C). However, clinicians should, in the future, be prepared to face the most challenging task of early diagnosis and treatment of such patients in clinical practice. However, the diagnosis of case No. 3 could be contested because hyperthermia in NMS is a must. Similarly catatonia, the harbinger of NMS which, also according to some, is iatrogenic lethal catatonia, remains the most difficult differentiating diagnosis of NMS. Bromocriptine, a DA agonist and an ergot by causing ergotism [2], may induce catatonia (though to my knowledge no such case report exists in the literature) which should be another differential diagnosis of NMS and in ergotism-induced catatonia, bromocriptine should never be used [2]. I disagree with the authors and propose classifying the sulpiride, the substituted benzamide and clozapine, as atypical neuroleptics rather than non-neuroleptics.

Of greater significance for preventive purposes is the recognition of risk factors for NMS. Several untested risk factors including young men (ages 20–40), nonschizophrenic psychotic and/or nonpsychotic states, rapid change in neuroleptic regime, rapid increase in use of higher doses, frequent addition and change to high potency neuroleptics and their frequent parenteral administration, the acute withdrawal of anticholinergics and dopamine (DA) agonists, use of DA depleting drugs, marked psychomotor agitation, organic brain diseases, primary hypothyroidism, dehydration, physical exhaustion, and debilitation have been suggested for the development of NMS. The four patients showed some of these susceptible factors including young age, agitation, rapid change in neuroleptic regime, exhaustion, and neurological disorders such as Parkinson disease. The obvious absence of diagnoses of other patients in this paper including polydrug abusers secondary or nonsecondary to other psychiatric disorders undermines the significance of this risk factor for NMS. Although these risk factors are tentative in nature, the authors [3] in a case controlled study have, however, reported some significant risk factors such as agitation, rapid change in neuroleptic regime, i.e., higher doses and rate of dose increase, and greater parenteral administration of high potency neuroleptics in mental patients with NMS. The most important implication is that neuropsychiatric patients should be evaluated for such risk factors and treated either with conservative doses of neuroleptics or alternative somatic therapy should be used to ameliorate agitation.

Regarding the etiology of NMS, in addition to postsynaptic DA blockade, DA depletion or decrease in DA release in basal ganglia, hypothalamus, and reticular activating system, other mechanisms such as the facilitative role of increased serotonergic [4] and noradrenergic [5] neurotransmission, and elevated myoplasmic calcium [6], hypercholinergic state following anticholinergic drug withdrawal provoking relative DA deficiency have also been considered. The induction of NMS by cocaine, which blocks the reuptake of dopamine into the presynaptic terminals, thus facilitating the action of dopamine on postsynaptic receptors, is an intriguing phenomenon and needs further investigation. Some investigators [7] have postulated that NMS possibly occurs among genetically predisposed individuals. Of extreme concern to the clinicians is the reintroduction of neuroleptic therapy among mental patients requiring antipsychotic medication but who have suffered from NMS. In a study involving neuroleptic rechallenges among patients who have NMS, Rosebush et al [8] found that 87% of the patients did not develop any recurrences of NMS. This possibly reflects that these patients did not have an inherent intolerence to neuroleptics. It was suggested that following complete resolution of neuroleptic malignant syndrome, the neuroleptic treatment could be reinstituted after a 15–day hiatus of neuroleptic therapy. However, about 15–30% of patients who suffer from NMS and may be further susceptible to developing this syndrome with the reinstitution of neuroleptic drugs needs to be studied in depth.

In conclusion, although NMS is a poorly understood, life-threatening complication of neuroleptic drugs, the early identification of several possible risk factors will help clinicians in detecting this problem earlier, in particular, by alerting them to patients who should be more carefully scrutinized for the possibility of developing NMS.

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Tumors of the Eye in Saudi Arabia and the State of Bahrain

To the Editor: I read with interest the paper on tumors of the eye in Saudi Arabia by Huaman and Cavender [1] and would like to comment on the design and data analysis of this study and offer, for comparative purposes, the figures of these tumors in the State of Bahrain.

The critique of the study conducted in Saudi Arabia comes mainly from the method used, in which the data sample was collected and analyzed and includes the following: (a) although the cases were classified according to the World Health Organization (WHO)-Histological Typing of Tumors of the Eye and its Adnexa, those from lacrimal glands were excluded from the study [2]. The interested reader is therefore left to speculate on origin of 13 adenocarcinomas (and 14 adenomas) cases, whether dermal, lacrimal or metastatic; (b) the WHO International Classification of Diseases for Oncology [3] classification of tumors of the skin of the eyelids and canthi to the skin and not to the eye. BCC of the eyelid is a skin lesion and is not different from that arising on the face or elsewhere in the body. On the other hand, if the aim of the study was to report the frequency of BCC of the skin of eyelids among the Saudi population because of associated environmental factors, then the number of patients with squamous cell carcinoma (SCC) of same site must also be recorded for comparative reasons. The trend in tumor registries is to record BCC separately from skin malignancies because their numbers tend to overinflate the incidence of skin cancer and underestimate the rates of malignancies of other sites; (c) it would have been more informative if the nationalities of the patients were analyzed because we are well aware of the number of Bahraini patients with various eye malignancies, particularly retinoblastoma, who are referred to King Khaled Eye Specialist Hospital (KKESH) for surgery and radiotherapy; (d) in accordance with the WHO recommendations [3], the figures on conjunctival (squamous) intraepithelial neoplasia (CIN) should have been dealt with separately from primary carcinoma since the lower grades may be the result of inflammatory response rather than truly neoplastic; (e) it is pointless to list the frequencies of benign tumors apart from the association of junctional conjunctival nevi and melanoma. World tumor registries do not record these neoplasms unless warranted. On the other hand, nevi and hemangiomata are long regarded as hamartomas rather than as neoplasms and the epithelial inclusion and noninclusion cysts mentioned in the paper as well as dermoid cysts, keratosis, verucae, histiocytosis, and xanthelasma are definitely non-neoplastic and their frequency should not appear in the paper even when referring to benign tumors.

During the period between 1952-1991, there were 3,536 Bahraini patients with histologically diagnosed malignant neoplasms in Bahrain, of whom only 27 (0.8%) had primary eye tumors. The regional topographical distribution of these tumors in accordance with the WHO International Classification of Diseases for Oncology was as follows: one melanoma of the ciliary body, six orbital tumors (four rhabdomyosarcomas and two non-Hodgkin lymphomas), three lacrimal gland malignancies (two adenocystic carcinomas and one SCC), ten conjunctival tumors (nine SCC and one melanoma), six retinoblastomas (two of whom were sisters), and one malignant melanoma of the choroid. During the same period there were also 44 Bahraini patients with noninvasive malignancies of whom seven (16%) had CIN (five squamous and one junctional nevus with features of noninvasive melanoma) and no metastatic tumors or malignancies of unknown sites in the eye. These figures on eye tumors are too small to draw a significant conclusion despite the length of the study and its inclusion of Bahraini patients only. It would be of interest to know the pattern of eye tumors in other parts of the Arab world and this further points out the need for establishing an Arab cancer registry.

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Wilson Disease in Saudi Arabia

To the Editor: We read with interest the paper by Ahmad et al [1] on Wilson disease in Saudi Arabia and would like to add the following comments: Wilson disease has an estimated prevalence of around 3/100,000 in many parts of the world [2]. Surprisingly, only a small number of known cases have been reported from Saudi Arabia. We reported the case of a family in which a 20-year-old female presented with the neurological manifestations of the disease while her 7-year-old sister had the hepatic form [3]. Recently, we treated a 25-year-old male presenting with the neurologic form, and in whom a magnetic resonance imaging (MRI) of the brain (Figure 1) revealed the typical appearance of striatal abnormal intensity. One of the patient's sisters also had Wilson disease. Although these patients were seen in different regions of Saudi Arabia, their families were originally from the same small town northwest of Riyadh.

In view of our interest in the epidemiology of Wilson disease, we would like to know the place of origin for the family reported by Ahmad et al [1]. Unfortunately, the places of origin were not specified for the seven cases previously reported from the King Khalid University Hospital (KKUH) in Riyadh [4]. If there is any geographi-

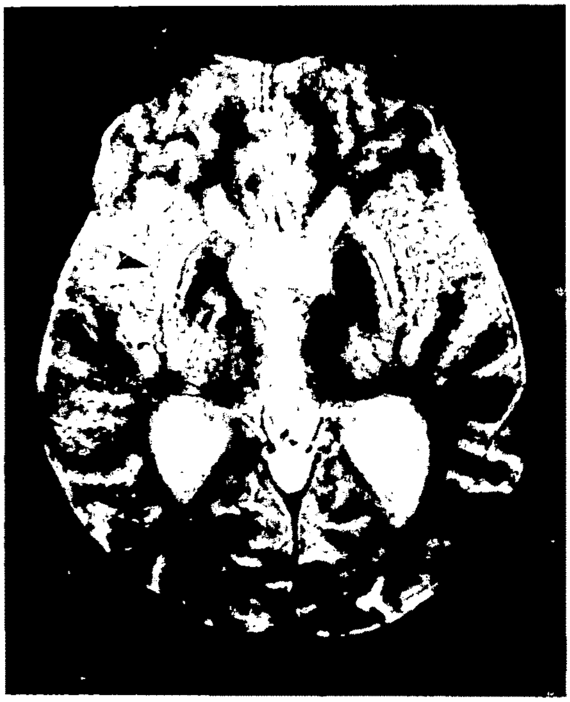

FIGURE 1. Bilateral high intensity signal of the putamen (arrow) on T2-weighted images highly suggestive of Wilson disease.

cal clustering of the disease in Saudi Arabia, this information would be interesting and useful to know. We agree with Ahmad et al [1] and Nazer [5], that the delay in diagnosis and institution of therapy in this disease is common. In addition to the protean presentations of Wilson disease, the generally dark color of the eyes in the Saudi population makes the clinical discovery of Kayser Fleisher ring particularly difficult. It is likely that Wilson disease is more frequent in the country than has been reported and that many cases remain to be documented.

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Reply

To the Editor: I would like to thank Drs. Awada and Al-Rajeh for their interest in our article entitled "Wilson disease in Saudi Arabia". Our family originated from a small town west of Riyadh (Addawadmi). It seems that these patients originated from the same area. Whether this is genetically or geographically determined would be of interest.

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Association of *Helicobacter Pylori* and Nonulcer Dyspepsia

To the Editor: We read with interest the article published in the *Annals* by Dr. Darwish [1] regarding the association of *Helicobacter pylori* and non-ulcer dyspepsia (NUD). We are concerned that the author did not include a control group of asymptomatic subjects in the study in order to validate the findings. This is an important consideration since Mahmood [2] demonstrated that *H. pylori* infection is extremely common among adult residents of Saudi Arabia. Furthermore, the article concludes that treatment with triple therapy (i.e., bismuth, amoxil and metronidazole) for a period of four weeks will "cure" patients with NUD.

The duration of follow-up of the treated patients was too short to claim a cure. Indeed, *H pylori* infection has proved difficult to eradicate [3]. At a one year follow-up after the cessation of medical treatment, the organism is eradicated in only 70% of subjects [4]. Therefore, without appropriate follow-up and in the absence of a control group, claims of a "cure" for NUD are not yet warranted.

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Reply

To the Editor: I would like to thank the authors for their comments. The study of Mahmood [1] included only those patients with non-ulcer related dyspepsia (NUD) and not the Saudi residents as a whole. He reported a 96.5% colonization rate by *Helicobacter pylori* (HP) among the studied NUD cases and that the antral biopsies obtained from these cases showed chronic gastritis. These documents support our findings [2]. Again, there are accumulating data from different studies [3–6] documenting the high correlation between HP infection and NUD as proved by histological findings of active chronic gastritis. This means that most of NUD cases have been colonized by HP. Clearance of HP ameliorates the dyspeptic symptoms [7] and improves histologically the gastric mucosa [8] in NUD cases.

Eradication of HP is difficult since the re-infection rate is significant because, at the moment, we do not know either the natural source, reservoir or the mode of transmission. Therefore, whatever the duration of follow-up would be, the long term cure rate of NUD will remain limited because we are unable to prevent reinfection during follow-up period.

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Osteoporosis: A Disease Looking For Recognition in Saudi Arabia

To the Editor: Osteoporosis, defined as a decrease in the bone mass, is an age-related disorder and is the most common metabolic disorder affecting the skeletal system. It afflicts more women than men. Most of the time, it is an asymptomatic process until a fracture occurs, which usually happens with mild trauma during the post-menopausal period.

Hip, vertebrae, distal radius and upper end of the humerus are the most common fracture sites associated with osteoporosis. Osteoporosis related fractures are seen with an increasing frequency. In the USA, up to 30% of all women over the age of 65 years have one or more vertebral fractures. In the USA, it is estimated there will be 500,000 hip fractures per year by the end of the century with a mortality rate of 50% one year following hip fracture. The financial burden of these fractures on the health care system is enormous; it is estimated that the total annual cost of hip fractures in the USA is $10 billion [1].

Bone mass reaches its peak by age 35–40 years among men and women. After the age of 40, there is a slow gradual bone loss until the time of menopause, when there is accelerated bone loss

[2]. This phenomena has been documented in different populations including the Saudis [3].

Estrogen deficiency is a known risk factor for developing osteoporosis and for increasing risk of fracture. Sex and race are other risk factors; Caucasian women run two and three times the risk of hip fractures during their lifetime as compared to Caucasian men and black women, respectively. Prolonged immobilization, long-term corticosteroid therapy, poor calcium and vitamin D intake are also recognized risk factors for osteoporosis.

In Saudi Arabia, 25-hydroxy vitamin D, which reflect body stores, was found to be significantly lower among females when compared with the age-matched males [4]. It was pathologically low among Saudi mothers and their neonates [5].

Osteopenia, shown on plain radiography, is an advanced stage for any preventive measures to be of value. Therefore, one of the areas that have contributed to the early recognition of osteoporosis is the new technique for non-invasive bone mass measurement at clinically relevant sites. Single photon absorptiometrometry was the early mode; which is useful for measurement at appendicular sites only. Other modes for mass measurements that are useful at axial skeleton are dual-photon absorptiometry, dual x-ray energy absorptiometry, and quantitative computed tomography. Based on sufficient data, the Advisory Scientific Board of the National Osteoporosis Foundation issued a statement summarizing the clear indication for use of the above techniques [6], including (1) estrogen deficiency; (2) vertebral radiography "spinal osteopenia"; (3) long-term corticosteroid therapy; and (4) asymptomatic hyperparathyroidism.

Several options for osteoporotic prevention are available at present. Adequate calcium intake needs to be initiated well ahead of the premenstrual state. Estrogen therapy for postmenopausal women was shown to slow the process of bone loss [7]. Fluoride therapy improved the axial bone mass; however, it was associated with an increased rate of vertebral fractures [8]. Injectable calcitonin was shown to improve bone mass [9]. However, the mode of administration limits its use. Only recently has nasal calcitonin become available. Cyclical (Etidronate) biphosphanate therapy was associated with improved bone mass and decreased rate of new vertebral fractures [10].

The problem of osteoporosis in Saudi Arabia has been overlooked until now. It is of paramount importance to identify the magnitude of the problem of osteoporosis and its related fractures in Saudi Arabia. This will be the cornerstone of setting up programs for screening high risk groups through non-invasive techniques and treatment at early stages of the disease with the aim at limiting disability and its impact on the national health resources.

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King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

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For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

King Faisal Specialist Hospital and Research Centre Academic Calendar for 1413H/1993G

King Faisal Specialist Hospital and Research Centre has scheduled the following Academic Calendar for 1992-1993G/1413H:

FMGEMS Examination	26-27 Rajab 1413 19-20 January 1993
Symposium on Nutritional Treatment and Intervention of Disease	4-5 Shaban 1413 26-27 January 1993
Symposium on Recent Advances in Diagnostic Radiology*	16-18 Shaban 1413 7-9 February 1993
USMLE (Step 2)	7-8 Shawwal 1413 30-31 March 1993
USMLE (Step 1)	18-19 Dhu Al Hijjah 1413 8-9 June 1993

For additional information, please contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7238; Fax: (01) 442-7237.

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المدونات الطبية السعودية

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المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي - جامعة الملك سعود، صندوق بريد ٢٩٢٥ - الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ - الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوَّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي:

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الرياض ١١٢١١ - المملكة العربية السعودية

المسئول عن الإعلان:
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فاكس: ٧٨٦٧٢٦٢ - ٠٨١

الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخه بأي شكل وبأي وسيلة سواء أكانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إليكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.

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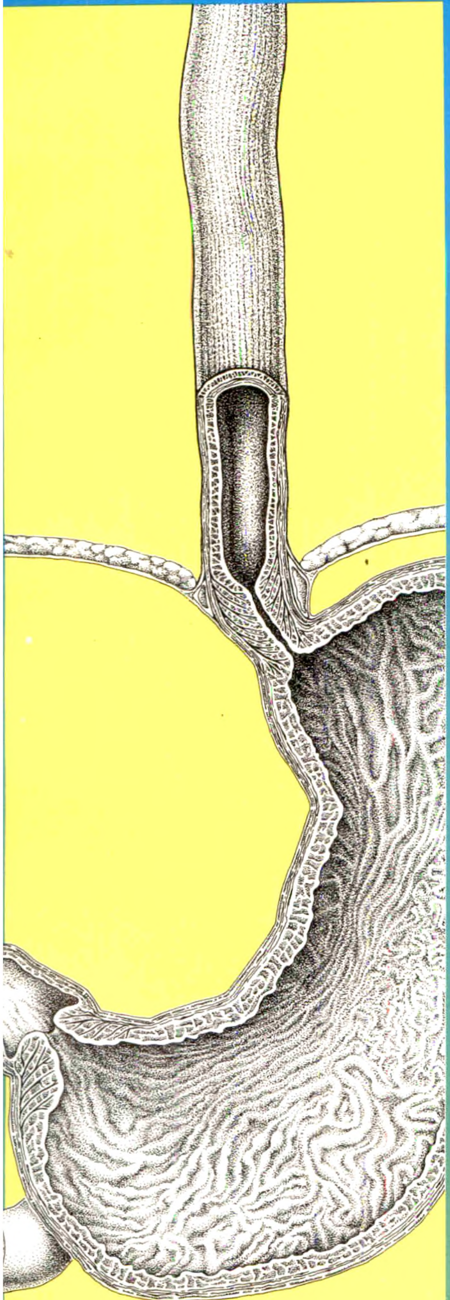

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